10 October 2019
EMA/562522/2019
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Neptra (EMEA/V/C/004735/0000)

INN: florfenicol / terbinafine hydrochloride / mometasone furoate

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

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Introduction

The applicant Bayer Animal Health GmbH submitted on 10 July 2018 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Neptra, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility for the centralised procedure was agreed upon by the CVMP on 16 February 2017 as Neptra contains a combination of existing active substances (florfenicol/ terbinafine hydrochloride/ mometasone furoate) one of which (terbinafine hydrochloride) was not authorised in a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

The applicant applied for the following indication: "For the treatment of canine otitis externa caused by susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*)".

The active substances of Neptra are florfenicol, an antibiotic, terbinafine hydrochloride, an antifungal and mometasone furoate, a corticosteroid to treat topical inflammation. The target species is dogs.

Neptra ear drops solution contains 16.7 mg/ml florfenicol, 16.7 mg/ml terbinafine hydrochloride and 2.2 mg/ml mometasone furoate and is presented in packs containing 2 tubes, 10 tubes and 20 tubes.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Tita-Maria Muhonen.

The dossier has been submitted in line with the requirements for submissions under Article 13b of Directive 2001/82/EC – a fixed combination application.

On 10 October 2019, the CVMP adopted an opinion and CVMP assessment report.

On 10 December 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Neptra.

Scientific advice

The applicant received scientific advice from the CVMP on 9 July 2015.

The scientific advice pertained to the submission of certain safety documentation in the dossier. The advice given by the CVMP was followed by the applicant.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system (DDPS)

The applicant has provided a detailed description of the pharmacovigilance system (Version 5.0 dated 02 July 2018) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form, primary and secondary packaging takes place within the EU. Batch release take place at KVP Pharma + Veterinaer Produkte GmbH Germany. The site has a manufacturing authorisation issued by the German Authority. GMP certification has been provided. The site was considered appropriately certified as complying with GMP requirements.

GMP declarations for all the manufacturing sites, for the active substances, are provided from the Qualified Person (QP) at the EU batch release site.

Overall conclusions on administrative particulars

The Detailed Description of the Pharmacovigilance System (DDPS) was considered in line with legal requirements.

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

The updated version of the DDPS was submitted in July 2018 for review in the centralised procedure for several products. Based on the outcome of the review the DDPS is considered acceptable.

Part 2 - Quality

Composition

The medicinal product is presented as an ear drops solution, in single-dose container, to be administered into infected ears of dogs for the treatment of otitis externa. It contains florfenicol, terbinafine hydrochloride and mometasone furoate as the active substances.

Other ingredients are propylene carbonate, propylene glycol, ethanol, Macrogol 8000, and purified water. Nitrogen is used to overlay the product filled into the tubes before sealing.

The product is available in single-use sealed laminated tube 1.5 ml with polypropylene cap and separate LDPE applicator nozzle, inside an outer cardboard carton containing 2, 10 or 20 tubes, as described in section 6.5 of the SPC.

Containers

The primary packaging is a white laminated tube 1.5 ml PE/Al/PE with a polypropylene screw cap for filling volumes up to 1 ml and separate white LDPE plastic adapter.

Specifications and test procedures for the 1.5 ml tube white PP screw are included in the dossier.

Satisfactory extraction studies of the containers, according to the Guideline on plastic immediate packaging materials (EMEA/CVMP/205/04), are presented to demonstrate the compatibility with the medicinal product.

Statements that the tube material is in conformity with Commission Regulation (EU) 2016/1416 on plastic materials and articles intended to come into contact with food and the plastic adapter complies with the FDA regulations CFR 177.1520 relating to the use of polyethylene items in contact with food are included.

In line with the "Guideline on Plastic immediate Packaging Materials" the supplier of the primary package was provided. The tube and the separate LDPE applicator nozzle are inside of a transparent

plastic blister in a folding box.

Development pharmaceutics

The objective of the development pharmaceutics was to develop an ear drops solution containing a combination of three known active substances of terbinafine hydrochloride, florfenicol and mometasone furoate.

The recommended dose to be administered is a single treatment of 1 tube per infected ear, corresponding to 1.0 ml of the ear drops, solution.

The proposed formula is a clear slightly viscous solution formulated with three active substances. The active substances are present in solution in the final product therefore physical characteristics of the solid active substances such as particle size or polymorphism are not expected to have an impact on bioavailability.

The excipients utilised within the formulation are well established and all are listed within the Ph. Eur. or in the USP. The list of excipients is included in section 6.1 of the SPC.

Additionally, nitrogen is used to overlay the solution before sealing the tubes to prevent the oxidation of the components.

Regarding the compatibility between components, formal stability studies of the finished product (18 months) and satisfactory stability studies for the bulk before filling the solution into the primary packaging (6 months) are provided.

The product is formulated free from antimicrobial preservatives and supplied in single-dose containers. As use of the product, for the treatment of otitis externa, is contraindicated when the ear drum is perforated, it is not required to be sterile according to the Ph. Eur. monograph for ear preparations (0652).

The selection of the manufacturing process has been discussed in accordance with the Guideline on development pharmaceutics for veterinary medicinal products (EMEA/CVMP/315/98). Critical parameters of the manufacturing process have been satisfactorily discussed. The repeatability and robustness of the manufacturing process were also demonstrated.

The antimicrobial effect of the chosen concentration of alcohol was discussed. The description of the development of the formulation is supported by sufficient data. The selected excipients are widely used in ophthalmic formulations already in the market. The lack of osmolality data is considered acceptable as the composition prevents accurate osmolality determinations. Osmolality is not considered crucial to local tolerance of the formulation.

Method of manufacture

The manufacture is a simple process of mixing the components at controlled temperatures, mixing times and speed. After that, a filtration is performed into a tightly closed storage container and overlaid with nitrogen.

A satisfactory flow chart of the manufacturing process is included.

The process could be considered to be a standard manufacturing process. The validation of the proposed manufacturing method has been conducted on three full scale batches.

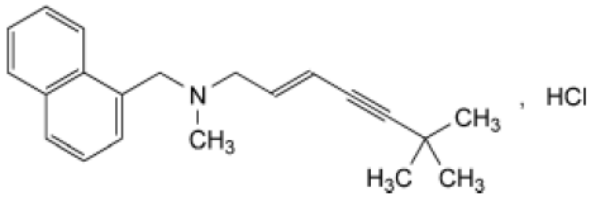
The manufacturing process and in-process controls have been described in detail and are adequate for this manufacturing process.

Control of starting materials

Active substances

Terbinafine hydrochloride

The chemical name of terbinafine hydrochloride is 2E)-N,6,6-Trimethyl-N-(naphthalen-1ylmethyl)hept-2-en-4-yn-1-amine hydrochloride and it has the following structure:



A copy of the relevant Ph. Eur. CEP is provided The Declaration of Access was completed with respect to the MAH.

The absence of use of material of human or animal origin in the manufacture of the substance has been declared.

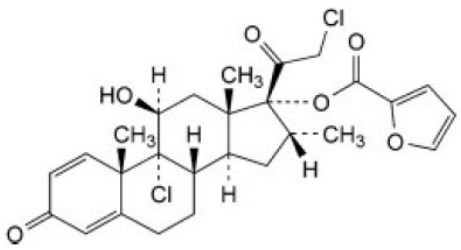
The active substance specification is stated to comply with requirements of Ph. Eur. monograph for terbinafine hydrochloride and includes a table of additional tests including those as listed on the CEP provided in respect of the material.

The dosage form is an ear drops, solution thus limits for particle size of the active substance are not deemed necessary because particle size is not liable to affect bioavailability. The microbial quality of the pharmaceutical product is controlled during final product release.

The container-closure systems and stability data have been assessed by the EDQM.

Mometasone furoate

The chemical name of mometasone furoate is 9,21-Dichloro-11β-hydroxy-16α-methyl-3,20-dioxopregna-1,4-dien-17-yl furan-2-carboxylate and it has the following structure:



A copy of the Ph. Eur. CEP is provided. The Declaration of Access was completed with respect to the MAH for Neptra Ear Drops Solution for Dogs.

The absence of use of material of human or animal origin in the manufacture of the substance has been declared.

The active substance specification is stated to comply with requirements of Ph. Eur. monograph mometasone furoate and includes a table of additional tests including those as listed on the CEP provided in respect of the material.

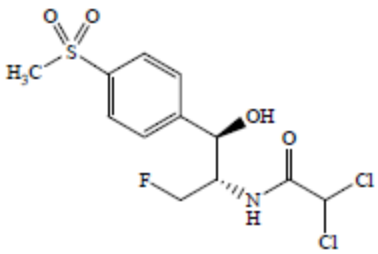
The dosage form is an ear drops solution thus the particle size of the active substance is not liable to affect bioavailability. The microbial quality of the pharmaceutical product is controlled during final product release and consequently the inclusion of a test for microbial quality is not considered necessary.

The container-closure systems and stability data have been assessed by the EDQM.

Florfenicol

Chemical Name of florfenicol is [R-(R*,S*)]-2,2-dichloro-N-[1-fluoromethyl-2-hydroxyl-2-[4-(methylsulphonyl) phenyl] ethyl] acetamide and it has the following structure:

CAS#: 73231-34-2



Florfenicol is not described in the European Pharmacopoeia or a pharmacopoeia of an EU member state and it is the subject of in-house monographs. Specifications developed for their control are presented.

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

The florfenicol molecule has stereochemical properties. As the active substance is presented in solution in the final product, physical characteristics of the solid active substances such as particle size or polymorphism are not expected to have an impact on bioavailability.

The characterisation of the active substance is in accordance with the Guideline on the chemistry of active substances for veterinary medicinal products (CVMP/QWP/707366/2017).

Regarding the potential impurities arising from the synthesis, clear information is provided regarding both organic and inorganic impurities, including detailed information regarding the impurities coming from the starting material. The in-process controls include a suitable control of impurities. Residual solvents have been appropriately discussed.

The proposed specifications of the florfenicol are in general considered appropriate for this active substance. The limits for related substances are in agreement with the Ph. Eur. General monograph 2034.

The methods are validated in accordance with the relevant VICH guidelines and are suitable for their intended uses. Appropriate batch analyses data is provided for three consecutive batches of the active substance. The information provided on reference standards is quite complete, and the standards are appropriately characterized.

Satisfactory information regarding the primary and secondary packaging has been provided.

Stability studies conducted at VICH conditions are presented. The selection of the controlled parameters is appropriate since they are stability-indicating. All tested parameters were within the

specification, and no significant changes in physical characteristics or impurity profiles was observed.

Satisfactory specifications are proposed by the medicinal product manufacturer.

The test methods have been validated and results of the validations have been provided. Satisfactory information about the reference standards used by the drug product manufacturer for their control of the active substance has been provided.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with their respective current Ph. Eur or USP monographs.

There are no novel excipients used in the finished product formulation.

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

Nitrogen is used to overlay the solution before sealing the tubes. Nitrogen is described in Ph. Eur. and compliance with the relevant monograph is confirmed.

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.

Valid TSE declarations from the manufacturers of the finished product have been provided.

Control tests during production

The critical steps and the control strategy are satisfactory.

Control tests on the finished product

The proposed release and end of shelf life specifications of the finished product includes the following: material, clarity and colour, identity of terbinafine HCl, florfenicol and mometasone furoate (HPLC), identity (IR), pH-value, density, viscosity, degradation products as well as assays for all three drug substances, uniformity of dosage units (mass variation) and microbial purity.

A clear description of the analytical methods is provided. A reference to the Ph. Eur methods is included for pH, density, viscosity, microbial purity and uniformity of dosage units (mass variation) testing. The description of the HPLC method is satisfactory and the system suitability criteria, defined for the assay of the three active substances, are in accordance with the criteria, defined in the general monograph 2.2.46., of the Ph. Eur.

The analytical method used to control the active substances and related degradation products is validated in accordance with the requirements of the VICH Guideline GL2 on Validation of analytical procedures: Methodology. Therefore, the method is considered suitable for the intended use and stability indicating. Satisfactory batch analysis results are provided for three industrial size batches. Information about the reference standards used by the drug product manufacturer for their control of the active substance is provided.

Stability

18 months stability data from three batches of the finished product stored at 5 ºC in a refrigerator, at 25 °C/60% RH and at 30 °C/75% RH was provided. Three batches were also stored for 6 months under accelerated conditions at 40 °C/75% RH in line with the requirements of the VICH GL3 (Stability testing of new veterinary drug substances and medicinal products). The batches of product were identical to those proposed for marketing and were packed in the commercial primary packaging. Three different batches of the drug substance florfenicol and two different batches of the drug substances mometasone furoate and terbinafine HCl were used in the production of the industrial scale batches.

Samples were tested for material, clarity and colour, identity of terbinafine HCl, florfenicol and mometasone furoate (HPLC), identity (IR), pH-value, density, viscosity, degradation products as well as assays for all three drug substances, uniformity of dosage units (mass variation) and microbial purity.

Specifications and analytical methods are those described in section 2E of the report. The analytical procedures used are stability indicating and have been appropriately validated.

In addition, two freeze and thaw studies are reported. The freeze and thaw study shows that the viscosity of the product exceeds the specification limit after storing at freezer condition, however, as this increase of viscosity is reversible by shaking which leads to a viscosity that meets the specification limits safely, the user instruction - "shake well before use" is included.

A photostability study is not provided but based on the nature of the proposed primary packaging the absence of photostability data is justified.

Finally, the applicant has confirmed that real time stability studies are on-going and will be continued at least up to the end of the shelf life.

Based on the provided data the proposed shelf-life of 18 months is justified. A 18 months shelf life with the storage condition "Do not store above 25 °C" is satisfactorily demonstrated.

Overall conclusions on quality

The medicinal product is an ear drop, solution in single-dose container to be applied to infected ears of dogs for the treatment of otitis externa. It contains florfenicol, terbinafine hydrochloride and mometasone furoate as the active substances.

Other ingredients are propylene carbonate, propylene glycol, ethanol, Macrogol 8000, and water purified. Nitrogen is used to overlay the product filled into the tubes before sealing.

It is presented in white laminated tubes with polypropylene cap for filling volumes up to 1 ml and it does not contain preservatives.

The description of the development of the formulation is clear and supported by data.

The process can be considered a standard manufacturing process and the description provided is satisfactory. Satisfactory data on the validation of the manufacturing process has been provided.

The information on the active substance, florfenicol, is provided according to the Active Substance Master File (ASMF) procedure. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF.

The stability results indicate that the active substance manufactured by the proposed supplier is

sufficiently stable and the proposed retest period is justified.

Copies of the Ph. Eur. CEPs are provided for the active substances, terbinafine hydrochloride and mometasone furoate. According to the EDQM Knowledge Database, the CEPs provided are the most current versions of the Ph. Eur CEPs available for the respective active substance manufacturers.

All excipients are well known pharmaceutical ingredients and their quality is compliant with their respective current Ph. Eur monographs or in monographs of the current NF/USP.

The release and shelf life specifications are acceptable and include parameters relevant to the dosage form.

Batch analysis results are provided for three industrial size batches.

Based on the provided data, an 18 months shelf life with the storage condition "Do not store above 25 °C" is satisfactorily demonstrated.

Part 3 – Safety

NEPTRA is a fixed combination of an antibiotic, an antifungal and a glucocorticoid. It contains florfenicol, terbinafine hydrochloride and mometasone furoate. The three active substances are already present in veterinary medicinal products for the treatment of otitis externa. However, it is the first time that these active substances are used as a fixed combination intended for treatment of external ear infections in dogs.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Toxicological studies

Neptra is a fixed combination veterinary medicinal product containing three active substances; florfenicol, terbinafine hydrochloride and mometasone furoate. All are already used in similar veterinary medicinal products for topical otic use in dogs but in different combinations.

Florfenicol has been used in food producing animals for more than 20 years, it is well established, and its toxicological profile has therefore been assessed by the CVMP and the applicant has referred to the MRL summary reports.

Mometasone furoate has been used in veterinary medicine just over 10 years and may therefore also be considered as an active substance that is well established in veterinary medicine according to Directive 2001/82/EC.

The toxicological profile of terbinafine hydrochloride is characterised by low oral acute toxicity. In repeated dose toxicity studies, the adverse liver, kidney and bladder findings were evident at the high dose. Terbinafine HCl was not teratogenic to rat. Terbinafine hydrochloride does not have any genotoxic potential.

Single dose toxicity

Acute toxicity of the 3 active substances is low. Terbinafine HCl and mometasone furoate showed low toxicity in rats, with oral and dermal LD50 higher than 2000 mg/kg bw. Florfenicol also showed low oral toxicity in mice and rats, with LD50 higher than 2000 mg/kg.

After oral or dermal exposure in rats, the acute toxicity of Neptra is also low (LD_{50} higher than 2000 mg/kg).

All pivotal single dose toxicity studies were conducted in compliance with GLP regulations and they followed OECD test guidelines.

Repeat dose toxicity

Florfenicol was tested in mice (13 weeks), rats (7, 14, 28 days and 13 and 52 weeks) and dogs (14 and 28 days, and 13 and 52 weeks). The toxic effects reported in rats were changes in haematological parameters and atrophy of the testes. In dogs, increased liver weights were seen. The dog was the most sensitive species with a no-observed-effect level (NOEL) of 1 mg/kg bw/day in the 52 weeks study. The toxicological acceptable daily intake (ADI) of 0.010 mg/kg (600 µg/person) was established from this NOEL.

Terbinafine HCl was investigated in several short-term studies, mainly in rats and dogs. The toxicity profile was very similar between the species and was consistent with liver and kidney effects. The OECD 13-week oral study in rat selected a NOAEL of 93.2 mg/kg bw/day in males and 138.2 mg/kg bw/day in females.

For mometasone furoate, it was concluded that the toxicity profile was typical of dose-related glucocorticoid effects. Target organs were thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy in rats and dogs. The lowest NOAEL reported was 1.25 µg/kg bw/day, obtained from an OECD 13-week oral study in rats.

The data contained in assessment reports of the FDA and CVMP for other VMPs may provide supportive data, however they cannot be considered to supply sufficient stand-alone information as they only contain summaries of toxicological studies. Therefore, the GLP-compliant 13-week oral toxicity studies, which were sponsored by the applicant can be considered to be the principal sources of repeated dose toxicity data of terbinafine HCl and mometasone furoate.

Tolerance in the target species of animal

The tolerance in the target animal is described under Part 4.

Reproductive toxicity

Florfenicol did not induce embryo/foetotoxicity or teratogenicity. High doses induced maternal effects and delayed ossification. The NOELs for maternotoxicity were 3 mg/kg bw/day for mice and 4 mg/kg bw/day for rats.

For terbinafine, developmental toxicity was studied in the rat. A no effect level (NOEL) of 50 mg/kg bw/day was determined for maternal toxicity (gravid uterus and the overall body weight gain reduction) and the NOEL for embryo-foetal developmental toxicity (increased incidence of supernumerary 14th ribs) was 50 mg/kg bw/day. Terbinafine HCl was not teratogenic to rat, even at

300 mg/kg bw/day in rat. The NOAEL determined (50 mg/kg bw/day) for rat was higher than the actual dose of administration for Neptra.

Mometasone furoate was not teratogenic to the rat. The no effect levels (NOAEL) of 140 µg/kg bw/day was determined for maternal toxicity (decreased bodyweight, bodyweight gain) and the NOEL for embryo-foetal developmental toxicity (no toxicity) was 400 µg/kg bw/day.

The reproduction study should aim to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the veterinary medicinal products or substance under investigation. No studies to examine the impact of terbinafine HCl or mometasone furoate on reproduction have been conducted by the applicant nor have relevant reports about such studies been found in public literature. All active ingredients of Neptra were only studied for developmental toxicity in rats. This is considered acceptable since Neptra is not intended for use in food-producing animals. The adverse embryotoxic and teratogenic effects of glucocorticoids in laboratory animals are well known.

Genotoxicity

Based on the negative results of *in vitro* (bacterial and mammalian cell systems) and *in vivo* (micronucleus and chromosome aberration tests in bone marrow) tests, the florfenicol, terbinafine HCl and mometasone furoate were not considered to have a genotoxic potential.

Carcinogenicity

Florfenicol was tested in carcinogenicity studies in mice and rats and was not concluded to be carcinogenic.

Terbinafine and mometasone were not tested in carcinogenicity studies. However, considering the negative results in genotoxicity, and that no preneoplasms were noted in the repeat dose studies, carcinogenicity deserves no further investigation.

Studies of other effects

Well conducted and recent studies were presented to assess skin irritation (terbinafine, mometasone and the final product), eye irritation (terbinafine, mometasone and the final product) and skin sensitisation (final product). For florfenicol, no specific studies were submitted, however studies conducted with the Neptra formulation covers also florfenicol.

Skin irritation: Terbinafine and mometasone showed no potential to produce skin irritation. The final product proved to be negative in the regulatory test for skin corrosion/irritation.

Eye irritation: Conflicting results were obtained for terbinafine, and eye irritancy cannot be excluded. The reason for inconsistent study results may be the test solvents used since animals exposed under the same test protocol and receiving the same active ingredient, but different formulations showed conflicting results. Therefore, it seems that eye irritation may be dependent more on the formulation than the active substance itself. The potential to cause eye irritation appeared to be rather low for mometasone furoate. When testing the final product, potential for eye irritation was obtained in three OECD *in vitro* studies and weak negative eye irritation was obtained in one OECD *in vitro* study, therefore, the overall conclusion was that the final product was considered to have serious eye irritating potential.

Skin sensitisation: terbinafine and mometasone were shown to have no skin sensitizing properties.

The final product did not present skin sensitisation in the maximisation test.

Excipients

The excipients are of low toxicity and listed as safe constituents in veterinary or human medicines and several of them are authorized for use as a food additive in EU.

User safety

An updated User Safety Risk Assessment has been provided. The qualitative and quantitative risks that may result from the exposure of the user to the VMP were characterised and addressed appropriately.

The product is an ear drop solution, with florfenicol, terbinafine HCl and mometasone furoate as active ingredients. Excipients of the product are currently used in veterinary and human medicine and their toxicological profile was provided.

The product is presented as a single dose tube (1 ml). It is a prescription-only medicine administered in a single treatment by veterinarian or under their close supervision.

The most likely potential routes of accidental contact with the product are those of dermal exposure during application and handling the treated dog and ocular and oral exposure via contact with contaminated hands. Accidental ocular, dermal and oral (hand to mouth) exposure is also expected as a result of unexpected reactions/ movements of the treated dog in response to instillation of the otic solution into the ear canal. Given the posology of the product, only occasional, low probability and short-term exposures are expected.

Neptra may have serious eye irritating potential; ocular exposure represents a relevant risk for local effects. Therefore, it is recommended that this veterinary medicinal product is administered only by veterinarians or under their close supervision to avoid the risk of accidental eye exposure for the owners.

The MAH performed the quantitative risk characterisation using the most relevant NOAELs and bioavailability factors derived for the individual ingredients considering the differences on the exposed subpopulation (adults and children vs. pregnant women). No risk is envisaged for pregnant women and women of child bearing potential (WCBP) as a result of use of Neptra whereas risk cannot be ruled out for children and adults during contact with the treated dog.

Accordingly, risk management and risk communication measures were included in the product information.

Environmental risk assessment

A phase I environmental risk assessment in line with the VICH GL 6 (Environmental impact assessment for veterinary medicinal products – Phase I, CVMP/VICH/592/98-Final) has been provided. The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals. It can therefore be concluded that no risks for the environment are expected to occur when Neptra is used according to the SPC.

Residues documentation

Not applicable.

Overall conclusions on the safety documentation

The acute toxicity of the three individual active substances is low, and it can be concluded that the acute toxicity of the combination product is also low.

Florfenicol was tested in mice (13 weeks), rats (7, 14, 28 days and 13 and 52 weeks) and dogs (14 and 28 days, and 13 and 52 weeks). Toxic effects reported in rats were changes in haematological parameters and atrophy of the testes. In dogs, increased liver weights were seen. The dog was the most sensitive species with a no-observed-effect level (NOEL) of 1 mg/kg of bodyweight in the 52 weeks study. The toxicologically acceptable daily intake (ADI) of 0.010 mg/kg (600 µg/person) was established from this NOEL.

Terbinafine HCl was investigated in several short-term studies, but mainly in rats and dogs. The toxicity profile was very similar between the species and was consistent with liver and kidney effects. The OECD study in rat selected a NOAEL of 93.2 mg/kg in males and 138.2 mg/kg in females.

For mometasone furoate, it was concluded that the toxicity profile was typical of dose-related glucocorticoid effects (FDA, 2004b). Target organs were thymus and adrenal glands with reduced weights accompanied by histopathological changes of lymphoid depletion and adrenal atrophy in rats and dogs. The lowest NOAEL reported was 1.25 µg/kg body weight, obtained from an OECD 13-week oral study in rats.

Florfenicol had no potential for embryo/foetotoxicity or teratogenicity. For terbinafine and mometasone, teratogenicity was elucidated providing information for one species (rat).

The three active substances were devoid of mutagenic/genotoxic potential in a battery of suitable genotoxic tests.

Florfenicol is considered to be devoid of carcinogenic potential. Terbinafine and mometasone were not tested in carcinogenicity studies. While carcinogenicity studies may be recommended if there is concern over carcinogenic potential, considering the negative genotoxicity, and absence of any evidence of preneoplastic lesions in repeated dose toxicity studies, carcinogenicity studies are not needed for terbinafine HCl and mometasone furoate.

The final product was shown to be non-irritant to skin, severe ocular irritant and a non-sensitiser of skin in recent well conducted studies.

An updated user risk assessment was provided. The qualitative and quantitative risks that may result from exposure of the user to the VMP were completely characterised and risk management measures were proposed. No risk is envisaged for pregnant women (and WCBP) whereas risk may take place for children and adults as a result of use of the VMP. Administration of the product should therefore be restricted to veterinarians (or under close supervision by the veterinarian) to avoid risk occurring at the moment of administration.

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

Neptra ear drops contain a combination of three active substances: florfenicol, an antibiotic (16.7 mg/ml), terbinafine hydrochloride, an antifungal (16.7 mg/ml), and mometasone furoate, a corticosteroid (2.2 mg/ml). The applicant applied for the following indication: "For the treatment of canine otitis externa caused by susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine hydrochloride (*Malassezia pachydermatis)*". The target species is dogs. The product is intended for single dose application (i.e. one dose per ear). This is the first time these active substances are used as a fixed combination intended for treatment of external ear infections in dogs.

Pharmacodynamics

Florfenicol is a synthetic broad-spectrum bacteriostatic antibiotic, structurally related to chloramphenicol and thiamphenicol, yet resistant to chloramphenicol transacetylases and therefore has a broader spectrum of activity than the aforementioned non-fluorinated amphenicols. It acts by inhibition of peptidyl transferase activity and subsequent microbial protein synthesis especially by binding to bacterial 70S ribosomes. Its use is well established in veterinary medicine.

A total of 4 published papers were provided to describe the pharmacodynamics/mode of action of florfenicol, out of which 3 papers were considered of high relevance for the application.

Terbinafine hydrochloride is an antifungal allylamine that exerts its activity via strong non-competitive inhibition of the fungal enzyme squalene epoxidase. Squalene epoxidase is a key enzyme of the ergosterol pathway, which is critical for the fungal cell membrane and fungal homeostasis.

A total of 4 published papers were provided to describe the pharmacodynamics/mode of action of terbinafine, out of which 2 papers were considered of high relevance for the application.

Mometasone furoate is a potent synthetic glucocorticoid. Like other glucocorticoids, mometasone furoate acts via binding to intracellular glucocorticoid receptors and modification of transcription of glucocorticoid-responsive genes.

One published paper of high relevance for the application was provided to describe the pharmacodynamics/mode of action of mometasone.

The mechanisms of action of the three active substances are considered to be appropriately described.

Pharmacological interaction of the active substances

The applicant conducted an *in vitro* non-interference study, which is assessed in section "Development of resistance", and concluded that no pharmacodynamic interaction exists between the three active substances against target pathogens. Regarding the lack of pharmacokinetic interaction, no clear conclusion could be drawn from the data presented; however, it is acknowledged that this part of the documentation should be interpreted with caution and considering the application as a whole. The main objective of the otic therapy is that the active substances exert their effects locally where the pathogens and inflammation are, so there should be a clear link between PK – PD – clinical effects and resolution of the clinical signs. Considering the above, the CVMP can accept the lack of information related to pharmacokinetic interactions.

The applicant also indicates that no evidence of pharmacological interaction between florfenicol,

terbinafine hydrochloride and mometasone furoate has been reported in the pharmacovigilance statement for an identical product approved in the USA under the trade name Claro.

Development of resistance

Limited information on the susceptibility of bacterial species isolated from canines to florfenicol is available in the literature. Regarding the activity of terbinafine against *M. pachydermatis*, a broad range of MIC values can be found in literature, and this is due to different methods as well as media and supplements used for MIC testing.

Bibliographic references concerning the known type(s) and mechanism(s) of acquired resistance to the active substances florfenicol and terbinafine were provided. Florfenicol resistance genes detected in staphylococci include cfr and fexA. Cfr modifies the RNA in the drug binding site (causing reduced affinity to chloramphenicol, florfenicol and clindamycin) and has been found in plasmids or other transmissible elements, whereas fexA codes for membrane associated efflux system (affecting both florfenicol and chloramphenicol) and has been found in both chromosomes and plasmids. Linkage of staphylococci-florfenicol resistance genes with virulence genes may occur and could explain persistence of resistance in the absence of selection pressure. FexA and cfr genes have been detected in staphylococci isolated from dogs with infection caused by MDR MRSA or MRSP and treated off label with injectable florfenicol.

Resistance to terbinafine in *M. pachydermatis* has been demonstrated to be caused by biofilm formation *in vitro*. However, biofilm forming capacity was not studied as part of sensitivity studies (this is not required by current guidelines).

Altogether, the information on resistance mechanisms of both pathogens is considered adequate; sufficient details, including standard phrases concerning identification of infecting organisms, have been added to the product information.

During the clinical development of Neptra, one Good Scientific Practices (GSP) and two GLP-compliant *in vitro* studies were performed according to CLSI guidelines to investigate the MICs of terbinafine against *M. pachydermatis* and of florfenicol against various bacterial species isolated from otitis externa cases of dogs included in the dose determination study and the pivotal EU clinical field study.

For florfenicol, an MIC_{90} of 2 µg/ml was determined for *S. intermedius* group isolates of the pivotal EU field study. A unimodal MIC distribution was seen, with a range of 1-4 µg/ml. Hence, the likelihood of a non-wild type subpopulation is considered low. These results are in line with some published data, where the MIC_{90} value was 4 µg/ml.

The *S. intermedius* group isolates of the dose determination study showed a higher MIC_{90} of 8 µg/ml (range 2-8 µg/ml, but in line with other publications. As for other bacteria tested for susceptibility, the *in vitro* efficacy of florfenicol against *Pseudomonas* spp. was poor, with MIC_{90} >128 µg/ml in both studies.

Terbinafine had fungicidal activity against *M. pachydermatis,* with an MIC_{90} of 2 µg/ml in both studies. The MIC distribution of *M. pachydermatis* was unimodal, thus the likelihood of a non-wild type subpopulation is considered low.

To conclude, the pre-treatment MIC values from the clinical studies are well in agreement with the literature for both pathogens; all the strains have been isolated in Europe in the last 5 years.

Since the breakpoints to determine antimicrobial susceptibility are based on plasma concentrations, the applicant argues that MICs are not useful for topical treatments. However, information on changes in MICs of bacteria isolated after the treatment is essential in assessing the risk of resistance development. Post-treatment MIC data is available at least for two field studies (EU and Japan) and the results showed that a small number of isolates on D7 to D28 after treatment were less sensitive to florfenicol compared to the control group or isolates on D0 in the Japanese field study. Regarding the possible selection of resistant bacteria, it should be noted that the MICs determined before and after treatment follow the same unimodal distribution and were always within the normal distribution of the wild type population observed in the clinical studies and described in literature.

To explore possible (non-)interference of florfenicol, terbinafine and mometasone in combination against canine otitis externa pathogens, a GSP *in vitro* study was conducted. Fractional Inhibitory Concentration Indexes (FICIs) calculated for the triple combination showed non-interference in 9/10 and antagonism in 1/10 of the *S. pseudintermedius* isolates. Although the FICI for this one strain indicated antagonism, it still had good susceptibility to florfenicol (MIC 0.5 µg/ml). Non-interference for *M. pachydermatis* was observed in all isolates (10/10). There was no synergism determined for any isolate of either *S. pseudintermedius* or *M. pachydermatis*.

Finally, some graphics in the pilot PK study have been used to establish the period of time for which the concentration of florfenicol and terbinafine in ear wash collections remains above the MIC_{90} (See section "Pharmacokinetics"). This allows the conclusion that the period of effect is approximately 7-11 days, and after that residual concentrations persist for an unknown period of time.

Bacterial and fungal susceptibility was explored in field studies on isolates taken between day 0 and day 28 and no resistance pattern was identified.

Taking into account the totality of the information and data provided, it can be concluded that the risk of emergence of resistance after the use of the Neptra can be considered low. In addition, adequate warnings related to the proper use have been included in the product information.

Pharmacokinetics

Recent scientific publications regarding the pharmacokinetics of florfenicol in dogs after intravenous, intramuscular and oral administration are provided in the dossier. Like in other species, florfenicol is rapidly absorbed in dogs after intramuscular and oral administration. It is quickly and widely distributed in well-perfused tissues and exhibits a low to moderate clearance. Elimination occurs quickly and, similar to other animal species, florfenicol amine is the main metabolite in dogs. No literature data regarding the pharmacokinetics of florfenicol following topical application in dogs has been provided.

The pharmacokinetic properties of terbinafine after oral administration to healthy Greyhound and mixed breed dogs were provided. Also, the metabolic capacity of Greyhound dogs was compared with that of Beagle dogs and it was concluded that Beagle dogs are particular rapid metabolisers in contrast to Greyhound dogs being slow metabolisers. No information regarding the pharmacokinetics of terbinafine HCl following topical application in dogs has been provided.

No information regarding the pharmacokinetics of mometasone furoate following topical application in dogs has been found following literature search.

The applicant provided two PK studies: one older non-GLP pilot study, and a second pivotal GLP-compliant study.

The first study was a pilot non-GLP study conducted to characterise the rate and extent of systemic absorption of the active substances and the rate of their clearance from the ear canal and it included serum and ear wash samples.

The concentrations of active substances in the external ear canal were established through analyses of ear wash samples. The highest values were found on D1 and concentrations seemed to drop thereafter. The last measurement was on D16, and at that time concentrations were 1390-5410 µg/l, <LOQ-471 µg/l and 922-2350 µg/l for florfenicol, mometasone furoate and terbinafine HCl, respectively. It is not known for how long the active substances persist in the external ear canal. With reference to the last timepoint (D28) for clinical and bacteriological assessment of the ears in the studies performed, the applicant has included adequate advice in the product information: "It is recommended not to repeat ear cleaning until 28 days after administration of the product".

Due to methodological reasons, this pilot study was inconclusive as to the systemic exposure of the active substances in healthy dogs.

However, the applicant has established the predictive period of time in which the concentration of florfenicol and terbinafine remains above the MIC_{90} values when considering the latest results of MIC testing for isolates from the EU field trial. Thus, the regression analysis for florfenicol demonstrated that the lower bound of the confidence interval fell below 4 µg/ml, *i.e., MIC_{90} for* S. pseudintermedius by 11 days post-dosing. The regression analysis for terbinafine demonstrated that the lower bound of the confidence interval fell below 2 µg/ml, *i.e., MIC_{90} for* M. pachydermatis*,* by 10 days post-dosing. In conclusion, when using the lower 95% bound of the confidence intervals, florfenicol and terbinafine above-MIC_{90} concentrations were observed for 10-11 days post-treatment.

Based on the ear wash regression analysis, the applicant considered that 17 days is an appropriate duration for the pivotal field study. This study duration adds 72 hours to the 14 days predicted as the time when florfenicol concentrations will fall below the MIC_{90} for *S. pseudintermedius,* or even longer depending on the interpretation of the analysis

It is acknowledged by the applicant that the analytical sensitivity in this pilot study was not sufficient to monitor the systemic exposure of mometasone. In this sense, the applicant made the appropriate modifications to the analytical methodology to increase the sensitivity of the method and, thus, to improve the capacity for quantifying the compounds (this optimised analytical method was used in the analysis of the samples in the pivotal PK study).

In the second, GLP compliant, pivotal PK study, the product was tested after a single dose at the target dose rate in the target species according to Guidelines for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99-Final). The actual mean dose rates were 15.7 mg florfenicol, 2.1 mg mometasone furoate and 15.7 mg terbinafine HCl, corresponding to a mean dose volume of 0.94 ml. This is approximately in accordance with the posology recommended in SPC 4.9; that is, 1 ml per ear, which contains florfenicol 16.7 mg, terbinafine hydrochloride 16.7 mg and mometasone furoate 2.2 mg.

Pharmacokinetic evaluation of the derived plasma concentrations was performed on the observed concentrations using non-compartmental methods. Evaluation was performed separately for each active substance contained in the test item. This non-compartmental methodology is considered appropriate, as recommended in the PK guideline.

The analytics were more sensitive in this study and the aim of studying the rate of systemic absorption was achieved; the validation of the analytical method was assessed and satisfactory results were concluded.

Mean plasma C_{max} of 1.73, 7.83 and 0.35 µg/l for florfenicol, terbinafine HCl and mometasone furoate, respectively, were achieved in 14.58, 17.08 and 1.25 h, respectively. On the last measurement on D28, two dogs still had low plasma concentrations of terbinafine HCL (0.211 and 0.100 µg/l). Plasma concentrations of florfenicol and mometasone furoate were below the LoQ earlier (last quantifiable concentration for florfenicol was 0.117 µg/l at 600 h (D25) in one dog and last quantifiable concentration for mometasone furoate was 0.065 µg/l at 336 h (D14) in one dog). In conclusion, the formulation of Neptra is long acting and low quantities of the active ingredients may be absorbed systemically for at least 14 days.

Considering the overall context of the formulation, and that the active ingredients are not intended to be absorbed (low quantities pass to the systemic circulation in variable amounts), it is considered that the pharmacokinetic profile of the veterinary medicinal product has been correctly addressed.

Justification of fixed combination

Neptra is a fixed combination of an antibiotic, an antifungal substance and a glucocorticoid. It is intended for treatment of canine otitis externa caused by susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*). Combinations of active substance classes with antibacterial, antifungal and anti-inflammatory activity are already established treatment principles for the treatment of external ear infections in dogs.

In line with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), the applicant claims that the combination of florfenicol, terbinafine hydrochloride and mometasone furoate in an ear drop solution is justified based on the fact that the disease is multi-factorial and treatment success generally requires antibacterial, antifungal and anti-inflammatory efficacy. Currently available treatment options require multiple administrations, and a single-administration dosage regimen by a veterinarian eliminates the risk for poor owner compliance.

The applicant has justified with literature the minimum dose volume for topical agents in the treatment of otitis externa as being 1.0 ml per application in large-breed dogs.

However, the fixed combinations guideline requires that every active substance in a fixed combination product must be indicated at the moment of treatment.

In this regard, the applicant states that the combination of an anti-inflammatory, an antibacterial and an antifungal agent is an established therapeutic principle treating otitis externa in dogs based on bibliographical references. To emphasize the need of every active substance at the moment of treatment, information has been added to SPC section 4.4 that the product is intended to be used only in canine otitis externa where a mixed infection with both target microorganisms has been demonstrated. This is also reflected in the indication for use (section 4.2 of the SPC).

Dose justification

The proposed dose of florfenicol, terbinafine and mometasone was established based on the findings of 5 dose determination studies.

As noted in the literature, the recommended minimum volume for topical agents to treat otitis externa is 1.0 ml per application in large-breed dogs. The applicant was asked to further justify the posology and the suitability of 1 ml volume for dogs of all sizes. The answer pertaining to single dose posology was considered acceptable as it related directly to the development history of the product (one single dose was shown to be efficacious) and the 3R's - it was not considered ethical to study

the efficacy of two subsequent doses as one dose was already proven to be effective. A single dose posology holds benefits relating to owner compliance.

The dose volume is the same as in other similar products, and the safety in smaller dogs is substantiated through clinical studies and pharmacovigilance information relating to the identical product registered in the USA under the tradename Claro.

Dose determination / finding studies

Four pilot field studies and one dose determination study have been submitted in support of dose determination.

Four pilot field studies have been conducted in the USA with naturally infected dogs as it has not been considered appropriate to investigate otitis externa in experimental laboratory studies. This is accepted. One study evaluated three different otic formulations (two emulsions containing chloramphenicol, terbinafine, betamethasone or florfenicol, terbinafine, mometasone, vs a solution containing florfenicol, terbinafine, mometasone), while the other three pilot studies evaluated the most successful of the three formulations (that is, the proposed formulation for authorisation). All four studies included a study protocol and statement of assurance (GSP standard).

The first exploratory study evaluated three different preliminary otic formulations. Two emulsions containing chloramphenicol, terbinafine hydrochloride and betamethasone and florfenicol, terbinafine hydrochloride and mometasone furoate, respectively (groups A and B) and one solution containing florfenicol, terbinafine hydrochloride and mometasone furoate (group C) were compared in a multicentre study involving 15 dogs with otitis externa in each group. On day 0, a physical examination and hearing tests were conducted, clinical scores (≥ 6 for inclusion) and swabs for bacterial culture and fungal cytology were obtained and then the ears were cleaned. Thereafter, each ear was treated with 1 ml of the respective IVP. Two follow-up visits with clinical evaluations on days 7 and 14 were conducted, with a hearing test and swabs for bacterial culture and fungal cytology taken if clinical cure (defined as a clinical score of ≤ 3) was not achieved. Most commonly, *Malassezia* organisms and *S. pseudintermedius* were identified. The effectiveness (clinical score ≤ 3) of a single dose of IVP-A, IVP-B and IVP-C administered at a dose volume of 1.0 ml/ear was 80.0%, 86.7%, and 93.3%, respectively. Based on the recalculation of the results taking into account only dogs harbouring both target pathogens, the effectiveness (clinical score ≤ 3) was 66.7%, 100.0% and 100.0% for IVP-A, IVP-B and IVP-C. The mean percentage reduction of Total Clinical Score (TCS) was 63.16%, 60.94% and 61.94%, respectively. There were no adverse events observed during the study.

Based on the results, the solution containing florfenicol, terbinafine hydrochloride and mometasone furoate was selected and a second pilot field study) was conducted in order to evaluate the effectiveness of this formulation compared to a placebo (the vehicle of the above mentioned solution without active ingredients) in 45 dogs with otitis externa. On day 0, a physical examination and hearing tests were conducted, clinical scores (≥ 6 for inclusion) and swabs for bacterial culture and fungal cytology were obtained and then the ears were cleaned. Thereafter, each ear was treated with 1 ml of the IVP or placebo. Two follow-up visits with clinical evaluations on days 7 and 14 were conducted, with a hearing test and swabs for bacterial culture and fungal cytology taken if clinical cure (clinical score of ≤ 3) was not achieved. *Malassezia* organisms and *S. pseudintermedius* were identified most commonly. Clinical cure was obtained in 24/30 dogs treated with the IVP and 2/15 dogs with placebo. The effectiveness of a single dose of IVP was 80.0% on day 14, whereas the effectiveness of the placebo was 13.3%. No statistical differences were evaluated. Based on the recalculation of the results taking into account only dogs harbouring both target pathogens, the

effectiveness (treatment success = TCS ≤3) was 83.3% for IVP and 16.7% for placebo (p=0.0801). There were no adverse events observed during the study.

After demonstrating the efficacy of the VMP in the above-mentioned studies, another pilot field study was conducted with an extended observation period to show efficacy after 30-35 days post treatment. No control group was included. Forty-one dogs were treated with Neptra. On day 0, a physical examination and hearing tests were conducted, clinical scores (≥ 6 for inclusion) and swabs for bacterial culture and fungal cytology were obtained and then the ears were cleaned. Thereafter, each ear was treated with 1 ml of the IVP. When both ears were affected, the right ear was chosen as the study ear. Two follow-up visits with clinical evaluations on days 14 and 30 were conducted, with a hearing test and swabs for bacterial culture and fungal cytology taken if clinical cure (clinical score of ≤ 3) was not achieved. *Malassezia* organisms and *S. pseudintermedius* were identified most commonly. Clinical cure was achieved in 34 of 38 dogs 30-35 days post-dosing. Based on the recalculation of the results taking into account only dogs harbouring both target pathogens, the effectiveness was 76.9%. There were two adverse events observed during the study, but neither was judged to be related to IVP administration.

A further pilot field efficacy study has been conducted in the USA to show superiority of the VMP compared to a negative control over a period of 30 days. Fifty-one dogs with clinical otitis externa from four study sites were treated with 1 ml of Neptra or a placebo. On day 0, dogs were examined and a clinical score based on erythema, exudate, swelling and ulceration of the ear canal was determined and had to be ≥ 6 for inclusion. A swab for cytology and one for bacterial culture as well as a clinical hearing test (clapping hands out of the dog's sight) were obtained and then the ear was cleaned with saline. In case both ears were affected, only the right ear was evaluated. Blood, serum and urine samples were collected for clinical pathology testing. Dogs were then treated with 1 ml of the IVP or placebo administered topically into the ear canal followed by a massage of the ear base. After 7 and 14 days, the dogs were clinically re-evaluated; the dogs which showed no improvement by at least two points were excluded and in those dogs blood, serum and urine samples were obtained again. All the other dogs were re-evaluated on day 30, clinically and with a clinical hearing test. The dogs with a score of ≤ 3 and no deterioration during the last 14 days were considered cured; all the other dogs were swabbed for cytology and bacterial culture. Clinical cures were obtained in 16/25 dogs treated with IVP and 5/24 dogs treated with placebo. The effectiveness conclusion is based on the statistical analysis demonstrating that the IVP was superior to placebo at p=0.06. Based on the recalculated data taking into account only dogs harbouring both target pathogens, clinical success was obtained in 57.1% of the dogs in IVP group and 20.0% in CP group (p=0.1618). Thus, the study failed to show superiority of the IVP over placebo. The study design was similar in the four studies and the evaluation dates are supported by the calculations to establish the predictive period of time stated in the pilot pharmacokinetic study.

In all four pilot studies described above, swabs for bacterial culture and fungal cytology were obtained at inclusion. However, no MIC data for the above mentioned pilot studies conducted in the USA are available. Studies have been conducted in the same year and country/region as the pivotal USA field efficacy study. Therefore, it can be assumed that the MICs in these pilot studies are comparable to the MICs determined in the USA field study. This assumption is supported by the fact that the MIC data for *S. pseudintermedius* isolated within the EU field efficacy study were well in line with data from literature and MIC values from the USA pivotal study. The MIC data for *M. pachydermatis* were slightly higher in EU compared to USA; however, they were in line with literature.

Additionally, one randomized, multicentre, blinded, blocked and controlled GSP dose determination study was conducted to evaluate the efficacy and safety of Neptra at three different concentrations.

Dogs with otitis externa in 10 veterinary practices in Germany were included and treated with either one of three different dose levels of the IVP: T1 (8.4 mg florfenicol, 8.4 mg terbinafine, 1.1 mg mometasone), T2 (16.7 mg florfenicol, 16.7 mg terbinafine, 2.2 mg mometasone), T3 (33.5 mg florfenicol, 33.5 mg terbinafine, 4.4 mg mometasone), or one commercial ear medication as positive controls (CP): T4 - 8.5 mg orbifloxacin, 0.9 mg mometasone furoate (as monohydrate), 0.9 mg posaconazole) or T5 - (2640 IU gentamicin as sulphate, 0.88 mg betamethasone and 8.8 mg clotrimazole). The IVP (solution) was administered only on D0 while the CP (suspension) was administered once daily (T4) or twice daily (T5) for 7 days. The dogs came for the first control visit on D7, i.e. one day after the last administration of CP. It was considered that blinding might have been affected by the fact that use of an oily suspension (positive control products) is often visible around the orifice of the external ear canal. However, this was accepted as no alternative positive control product without this feature was available. Dogs were clinically evaluated at days 0, 7, 14 and 30, cultures and cytology were obtained at days 0, 14 and 30. Otitis score (OS) was determined by evaluating erythema, swelling, dermal alterations, discharge, malodour, and scratching from 0 (absent) to 3; at inclusion, this score had to be ≥ 6 and bacteria or yeast had to be cultured or cytology smears had to show at least two *Malassezia* yeasts per ocular field. The primary efficacy criterion was the percentage of dogs clinically cured at day 14 (based on an OS of ≤ 1 and an OS ≤ 3); the secondary criteria were the percentage of dogs clinically cured at day 30, number of dogs with clinical relapse, bacterial and fungal cure, % of bacterial relapse, the time to cure, the general condition score and the number of animals removed by day 7 due to treatment failure.

Two serious adverse events (SAEs) were documented during the study, which were considered as not being related to the study treatment.

Regarding the efficacy results in the ITT population, they were not notably different to the results in the PP population. In relation to the primary efficacy endpoint, when it was based on an OS ≤ 3, the differences between all treatment groups were not statistically significant. On the contrary, when the efficacy endpoint was based on an OS ≤ 1, a statistically significant difference between T1 (8.4 mg florfenicol, 8.4 mg terbinafine, 1.1 mg mometasone) and T2 (16.7 mg florfenicol, 16.7 mg terbinafine, 2.2 mg mometasone), in favour of T2, was observed on Day 14±2, but the efficacy percentages were much lower compared to those based on an OS ≤ 3. The applicant stated that the percentage of cured animals with an OS of ≤1 was relatively low in all groups due to the maximum score at inclusion, which varied between 15 and 17 within the 5 treatment groups. Most studies evaluating otitis externa consider a clinical score of ≤ 3 sufficient for clinically satisfactory response. The CVMP agrees that an OS ≤ 3 as primary endpoint of efficacy is representative of a clinical cure.

In addition, the choice of the Neptra final formulation (T2) was supported by several secondary efficacy criteria. There were also observed some significant differences between groups in favour of T3, but given that this group tested the highest dose, the possibility to cause adverse effects might be increased.

No literature has been presented specifically in support of the concentration of each active substance in the formulation. In two studies, different strengths were compared. In one of the studies the proportion of active substances compared to each other remained the same (0.5X, 1.0X and 2.0X the final strength).

Two of the five studies submitted evaluated different doses of the formulation, whilst in the other three studies the final formulation was used.

It is noted that the inclusion criteria set for these studies did not include the necessity of a mixed infection (*S. pseudintermedius* + *M. pachydermatis*). Nevertheless, all the results were recalculated taking into account only the dogs harbouring both target pathogens. Even though the results from two studies failed to show superiority of the IVP compared to placebo, the recalculated data was overall supportive for the chosen formulation and dose.

Therefore, the choice of the formulation can be accepted.

Dose confirmation studies

The applicant has not conducted dose confirmation studies and justified this omission by the inclusion of several dose finding studies in the dossier. It should be noted that among the five dose determination studies, two studies tested the final formulation against placebo, whilst one study only tested the final formulation (no control group was included in the study).

According to the Guideline for the demonstration of efficacy for VMPs containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1), dose-confirmation studies may be waived if all of the following criteria are fulfilled:

- the conditions of the dose determination studies are representative of the field conditions in terms of the type of infection and the animals involved,
- the susceptibility pattern for any challenge strain used for dose determination is relevant for the field situation,
- a clear dose-effect relationship is documented as supported by adequate dose determination data,
- the dose determination data allows for the selection of one appropriate dose level,
- the dosing interval and the number of administrations is adequately justified.

Omission of dose-confirmation studies can therefore be accepted based on the above criteria.

According to the above-mentioned guideline, in dose confirmation studies, "when naturally infected animals are used, infection with the relevant bacterium(a) should be confirmed through appropriate sampling procedures and susceptibility testing of isolates should be performed". As mentioned, the applicant did not conduct any dose confirmation studies and justified this by the number of dose determination studies provided. These pilot studies have been conducted in the USA where it was not mandatory to perform MIC determination within this kind of exploratory studies. However, the MIC values would likely fit into the MIC range observed in the pivotal USA field study. In the European dose determination study, MIC data for the pathogens isolated pre-treatment have been determined and they are considered to be in line with the available literature and the data of the pivotal EU field study.

Therefore, it is considered that the studies submitted by the applicant are sufficient to justify the omission of dose confirmation studies.

Target animal tolerance

The safety and target animal tolerance of Neptra was closely investigated within two TAS studies: a pilot target animal safety study) and a pivotal FDA GLP-compliant target animal safety study; this study also meets OECD requirements, with some exceptions. In addition, safety data was also obtained from the two pharmacokinetic studies, four pilot field studies, the dose determination study and the three field studies conducted in Europe, the USA and Japan.

The non-blinded pilot safety study was designed to establish *in vivo* safety (including adrenocorticotropic hormone (ACTH) stimulation response) of Neptra prior to conducting the pivotal TAS study. The effects of a dose 5 times higher than the recommended dose of 1 ml per ear were evaluated as compared to a saline-treated control group.

After 3 weekly administrations of 5X the recommended dose, the test product induced slight erythema in one or both ears of 3 different dogs post dosing, which returned to normal within 48 hours. These adverse events were considered related to the treatment. Fluid loss and drip was observed in various animals after the application of the product.

In both of the 5X recommended dose treatment groups (dosed three times at one week or two week intervals), a decrease in cortisol level after ACTH stimulation was observed. Moreover, statistical significant differences were observed between both treatments and placebo group for haematology, clinical chemistry, urinalysis, and cortisol values, but these findings were not associated with clinical signs. These findings are consistent with pharmacologic properties of corticosteroids and are listed in section 4.10 of the SPC.

In the GLP-compliant pivotal target animal safety study, the tolerability of the test article was evaluated after intra-aural administration to juvenile healthy dogs (4 males and 4 females per group) 3 times every 2 weeks (days 1, 15, 29) at doses representing 1X, 3X and 5X of the intended therapeutic dose. The product was administered in volumes of 1 ml per ear every 2 hours until the desired volume was achieved. The control group dogs received a total dose of 10 ml (5 ml/ear) sterile 0.9% sodium chloride solution. The study was designed and conducted according to VICH GL43.

The study was blinded with respect to group designation. During the acclimatization period, food consumption decrease was observed in all males in control and 3X and 5X groups, however this was not associated with a decrease in the bodyweight gain.

The applicant has performed hearing tests (clapping test) and pathological-anatomical post-mortem studies on the auditory apparatus. The clapping tests were conducted by technical staff in a quiet area by clapping hands from a position not visible to animals and from such a distance that the animals would not react to air currents created by hand clapping. It is noted that a clapping test is not a very sensitive examination and does not enable to detect e.g. unilateral hearing deficits, however, according to the results of this TAS study, no product-related findings were noted at physical examinations and no relevant histopathological changes were noted post-mortem in the ears. Nonetheless, it was considered appropriate to include in the product literature the same warning concerning hearing loss or signs of vestibular dysfunction that is already included in the product literature for the identical product approved in the USA (Claro).

No IVP-related findings were noted at physical examination or hearing tests other than wet ears/clear discharge seen in animals given 1X (4/8 animals, Day 29), control (wet ears in 1 animal on Day 15) and variably on Days 1, 15, and/or 29 in all animals given 3X or 5X.

It is agreed that the main findings seen at 1X the recommended therapeutic dose (decreases in cortical response to ACTH stimulation, decreased absolute lymphocyte and eosinophil counts, and decreased adrenal weight) and at 3X and 5X the recommended therapeutic dose (RTD) (increased neutrophil counts [5X males only], increased cholesterol) were due to the glucocorticoid component of the combination; these findings are also supported by literature. Post-mortem test article-related findings were noted in the adrenal cortex and thymus and this is also supported by published literature. This information has been included in sections 4.5 and 4.10 of the SPC. Other findings seen at 3X and 5X the RTD (minimally increased total protein concentration and minimally to mildly

decreased inorganic phosphorus concentration) have also been included in the SPC.

Due to the systemic glucocorticoid-related effects, a warning is included in SPC section 4.5 to use the product with caution in dogs suffering from endocrinological disorders.

Apart from the two TAS studies, the applicant has summarized the results of ten studies submitted regarding the tolerance in the target species. The studies demonstrated the safety of Neptra in the treatment of otitis externa under laboratory and field conditions, with the respective observation period varying from 14 up to 35 days after treatment. The adverse events which occurred during the ten studies have been discussed in detail in the respective study reports and are summarized as follows: general adverse events observed after treatment with Neptra were digestive tract disorders (diarrhoea, intestinal disorder not otherwise specified (NOS), emesis) in 11 cases, ear and labyrinth disorders in 3 cases, eye disorders (eye redness, conjunctivitis) in 5 cases, musculoskeletal disorders (arthritis, lameness) in 2 cases, renal and urinary disorders (urinary tract disorder NOS, urinary incontinence) in 3 cases, respiratory tract disorders (bronchitis) in 2 cases, skin and appendages disorders (dermatitis and eczema, bacterial skin infection, pruritus) in 5 cases and systemic disorders (anorexia, lethargy, lipoma, pale mucous membrane, trauma and unrelated death (coumarin intoxication)) in 7 cases. None of these adverse events were considered as being treatment related.

The FDA published on 6.12.2017 a warning concerning eye injuries in both dogs and humans reported with the use of Osurnia and Claro. Reports in dogs included corneal ulcers, eye irritation, conjunctivitis, squinting, and eye pain. Further concerns regarding corneal ulcers but also middle ear inflammation and irritation with subsequent effects on cranial nerves, neurogenic keratoconjunctivitis sicca, Horner's syndrome and facial paralysis were also expressed. According to the FDA, there appears to be some cranial nerve damage and tympanic membrane rupture, even when verified as intact through visual inspection.

Terbinafine HCl is an active ingredient in Neptra (and the identical product Claro registered in the USA), as well as in Osurnia, and studies showed that it has ocular irritation potential. The applicant was requested to provide clarification on the adverse events relating to eye disorders and propose risk management and communication measures. The applicant has provided collated results of Claro adverse events relating to eye disorders; such adverse events were very rarely reported in dogs in the USA, and the applicant proposed some slight amendments to the SPC to prevent eye contact with Neptra during the administration phase of use.

The applicant provided overall pharmacovigilance data on the identical product sold in the USA (Claro) from market introduction in 2015 until (June) 2019. Adverse events reported, with a probable or possible causality assessment, were very rare and in all cases non-serious. These adverse reactions have also been included in the product information for Neptra.

Based on the data provided, it is concluded that the product is generally well-tolerated at the recommended dose. However, typical glucocorticoid treatment-related symptoms have been found as the most prominent findings. Decreased cortisol levels were observed after product administration in the tolerance studies. The applicant was requested to explain how the dogs recover from a hypothalamic pituitary adrenal (HPA) axis suppression of the magnitude observed in the pivotal TAS study as this was not investigated in the field studies. The applicant provided literature data which, in combination with study results, allowed concluding that the expected recovery in healthy dogs would be within 1-2 weeks after treatment.

An accidental over-dosage is extremely unlikely as the product is provided as single dose unit (tubes delivering 1 ml) and the administration is performed only by veterinarians or under their close

supervision.

Clinical field trials

The applicant has submitted 3 field trials in order to demonstrate the efficacy on Neptra for the treatment of canine otitis externa caused by susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*). One study was conducted in Europe, the second in the USA and the third in Japan.

The first study, conducted in Europe, was a pivotal, multicentre, randomized, fully blind, positive controlled parallel group design study, conducted in dogs to evaluate the efficacy and safety of the product in the treatment of acute clinical otitis externa (OE) and acute exacerbations of recurrent OE (erythematous, ceruminous and purulent forms only) under field conditions in Europe at the proposed dose (pipette with 1 ml of solution containing 16.7 mg florfenicol, 16.7 mg terbinafine hydrochloride and 2.2 mg mometasone furoate). The study was conducted in 20 veterinary practices located in different geographical locations in Germany and Hungary and adhered to GCP. Two hundred and ninety dogs were initially allocated, 286 were included in the ITT population (safety evaluation) and 262 in the PP population (efficacy evaluation); the dogs (137 females and 149 males; 224 purebred breeds and 62 mongrels) were aged from four months to 15.75 years and weighed from 3.04 kg to 68.00 kg.

A veterinary medicinal product authorised for the treatment of acute otitis externa and acute exacerbations of recurrent otitis externa in dogs was used as positive control in this study.

As eligibility criteria, dogs enrolled on Day 0 (+1 day) had to present clinical signs of otitis externa (Total Clinical Score (TCS) ≥ 5); at inclusion, the dogs had their details recorded, underwent a veterinary examination and samples for bacteriological, mycological and cytological analyses were collected. The dogs were re-examined on Days 7 (+1 day), 14 (+5 days) and 28 (+8 days) to assess the general condition and the clinical signs of OE. Further samples for bacteriological, mycological and cytological analyses were taken on Days 14 (+5 days) and 28 (+8 days) and in case of premature removal. The success of treatment was scored at the end of the study.

The primary efficacy criterion was the percentage reduction of TCS from Day 0 to Day 28 (+8 days), which was calculated for each dog in each treatment group. Two-sided 95% confidence intervals for the difference "IVP – CP" in the mean percentage reduction of TCS were calculated. The IVP was considered non-inferior compared to the CP if the lower limit of this confidence interval was greater than -15 percentage points (pp) (non-inferiority margin = 15 pp).

The secondary efficacy criteria were mean percentage reduction of TCS from SD 0 to 14, clinical (treatment) success (TCS ≤ 3), clinical relapse, bacteriological cure at SD 28, bacteriological relapse at SD 28, fungal response at SD 28, decrease of cytological counts at SD 28, investigator assessment of treatment success.

Out of the 286 dogs included in the ITT population, 145 were treated with Neptra and 141 were treated with the control product. However, since not all the animals included in the study harboured both target pathogens, the applicant was requested to recalculate the results taking into account these dogs only (IVP n=43, Group 1; CP n=45, Group 2).

According to these recalculated results, the mean percentage reduction of TCS (primary efficacy criterion) from day 0 to day 28 was 70.57% in Group 1 and 74.19% in Group 2, with a mean "IVP – CP" difference in percentage points of -3.62 pp and a lower limit two-sided 95% CI value of -14.08 pp. No significant difference between groups was observed.

The results for bacteriological and fungal cures were 62.8% and 32.6%, respectively, for Group 1 and 86.7% and 53.3% for Group 2, with a mean "IVP – CP" difference of -23.9% pp and -20.8% pp, respectively. Significant difference (p=0.0135 and p=0.0562) between the groups was observed.

Related to this point, the applicant has also provided the proportion of dogs that had a clinical cure (total clinical score of ≤3 on day 28) and no neutrophils present on day 28; these percentages were 72.1% for dogs in Group 1 and 80.0% for dogs in Group 2; the difference was not significant (p=0.4572) by Fischer´s exact test. Taking into account the cytology results, it can be assumed that most of the post-treatment isolates can be considered as commensals.

Regarding the secondary efficacy criteria for dogs which harboured both target pathogens, i.e. clinical success on day 28, clinical relapse, re-isolation of bacteria, bacteriological relapse, fungal response and decrease of cytological counts, these were also not significantly different between the two groups after 28 days.

MIC values for *S. pseudintermedius* and *M. pachydermatis* pathogens isolated in this study were determined and the results are presented in section *Development of resistance* above.

The tolerance of the IVP was also studied in this trial. 145 of 286 dogs (ITT population) were treated with the proposed IVP and five adverse events were reported; the 141 dogs treated with the CP showed a slightly higher number of adverse events. The adverse events reported in the IVP group were: conjunctivitis 1 (0.7%), diarrhoea 1 (0.7%), intestinal disorder NOS 1 (0.7%), pale mucous membrane 1 (0.7%) and pruritus 1 (0.7%). In the control group, the adverse events reported were: conjunctivitis 1 (0.7%), dermatitis and eczema 2 (1.4%), desquamation 1 (0.7%), emesis 2 (1.4%), erythema 1 (0.7%), otitis externa 1 (0.7%), pigmentation disorder 1 (0.7%). No serious adverse events were reported during the study. The observed adverse reactions are considered not to be treatment-related and therefore are not listed in SPC section 4.6.

No blood, serum or urine samples were collected during the study. The applicant based this decision on the results of the tolerance studies and the observations made during the USA pivotal field study, where it was concluded that glucocorticoid-related changes are not expected after single use of the product. This explanation was deemed acceptable after evaluation of blood and urine results obtained additionally in one of the USA pilot field studies.

Taking into account the recalculated results of this pivotal field study by including only dogs harbouring both target pathogens, the non-inferiority of the product Neptra when compared to a positive control can be accepted. The study results showed that Neptra was efficacious and safe to use when compared to a positive control.

In support of the pivotal EU clinical study, the applicant has submitted another pivotal clinical study conducted in the USA, which aimed at evaluating the field safety and effectiveness of a single administration of Neptra over a minimum period of 30 days for the treatment of canine otitis externa caused by susceptible strains of yeasts and bacteria when administered under actual use conditions. The study was conducted according to Guideline on Good Clinical Practices VICH GL9.

Dogs enrolled on Day 0 (+1 day) had to present clinical signs of acute clinical confirmed bacterial and/or yeast infection. The Total Clinical Score (TCS) required for inclusion was ≥ 6. Infections were caused mainly by *M. pachydermatis, S. pseudintermedius, Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli,* and beta-hemolytic streptococci.

Laboratory endpoints (routine haematology, urinalysis variables and serum chemistry variables) were assessed at Day 0 and Day 30 visits.

A total of 221 dogs were enrolled in the study, with 183 dogs being used in the efficacy evaluation. Of these 183 dogs, 120 received the IVP and 63 received a negative control product (CP). Since not all the animals included in the study harboured both target pathogens, the applicant was requested to recalculate the results taking into account only these dogs (IVP n=67; CP n=27).

When re-calculating the results of this study, which compared Neptra to a negative control, a significantly superior clinical response was shown regarding the primary endpoint "mean percentage reduction of TCS from Day 0 to Day 28 per protocol population based only on dogs harbouring both target pathogens at baseline" for dogs included in the IVP group (76.99%) compared to the dogs in the negative control group (49.46%), with a p-value of 0.0009.

For the haematology analysis, no statistically significant differences existed among any of the variables HGB, MCV, RSC, WBC. All mean values were within the normal ranges. For the serum chemistry, the only variables with statistically significant differences were calcium, chloride, cholesterol, Na/K and phosphorus. All mean values were within the normal ranges.

There were no serious adverse events reported in the study and all AEs observed during the study were considered as not treatment related.

In this study, the applicant also submitted the MIC determination results and bacteriological and mycological isolate counts from day 0. The MIC values reported in this study were not notably different than those reported in the pivotal field study conducted in Europe, therefore these results can be used in support.

The results of the study also show that Neptra is safe and efficacious when used for the treatment of canine otitis externa.

A third, GCP-compliant, positive controlled field study was conducted in 30 veterinary clinics in Japan. The study design was similar to the other two field studies submitted. An otic score based on erythema, swelling, exudates, and/or erosion/ulceration was used for the evaluation of efficacy. Dogs were treated with the recommended dose.

When the results were recalculated taking into account only the animals which harboured both target pathogens, the sample size was reduced to 7 dogs in the IVP group and 9 dogs in the CP group. The mean percentage reduction of TCS (primary efficacy criterion) from day 0 to day 28 was 72.15% in IVP group and 79.31% in CP group, with a mean "IVP – CP" difference in percentage points of -7.16% pp and a lower limit one-sided 95% CI value of -31.19 pp. No significant difference (p=0.5313) between groups was observed. Similar findings to the other studies in the haematological parameters and chemistry were found.

The conclusions of this study are similar to the other two studies submitted; however, due to the very limited sample size, the results may be regarded as supportive only.

Only gastrointestinal signs were recorded as AEs in both groups and considered as not treatment related. As the number of animals was markedly reduced after recalculation of the results, the study results are only considered as supportive.

In the clinical studies provided with this application, the last evaluation of efficacy was made on days 30-35. It is acknowledged that a longer follow-up period would have been preferable in order to examine possible relapses. However, otitis externa is a multi-factorial disease and usually has an underlying cause. If the underlying cause is not adequately treated, relapses may easily occur and it can be difficult to identify the cause of the relapse (e.g. allergy/atopy alone despite effective treatment or in combination with ineffective pharmacological treatment). The clinical studies were

designed to show non-inferiority to positive control products or superiority against a negative control product in the treatment of acute otitis externa. Both trial designs are considered to be in accordance with the Guideline for the demonstration of efficacy for VMPs containing antimicrobial substances (EMA/CVMP/627/2001-Rev.1).

To conclude, both pivotal field studies (EU and USA) showed that the product was efficacious for the treatment of acute canine otitis externa or acute exacerbations of recurrent otitis caused by mixed infections of susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*) and in this regard the indication was amended accordingly. The studies showed that the product was well-tolerated under field conditions and that clinical cure was non-inferior to a similar product or superior to a negative control product.

Overall conclusion on efficacy

Pharmacodynamics

Neptra contains 3 active substances, an antibiotic, an antifungal substance and an anti-inflammatory component.

Florfenicol is a synthetic broad-spectrum antibiotic which acts by inhibition of peptidyl transferase activity and subsequent microbial protein synthesis.

Terbinafine is an antifungal allylamine which exerts its activity via strong non-competitive inhibition of the fungal enzyme squalene epoxidase.

Mometasone furoate is a potent synthetic glucocorticoid which acts via binding to intracellular glucocorticoid receptors and modification of transcription of glucocorticoid-responsive genes.

The applicant justified the combination by the fact that the disease is multi-factorial and treatment success generally requires antibacterial, antifungal and anti-inflammatory efficacy, this being considered an established treatment principle. The main advantage claimed for the combination is a single-administration dosage regimen by a veterinarian.

Resistance

Neptra is a combination of three active substances which has not been used in veterinary medicine before. Low concentrations of active substances persist in the external ear canal for an unknown period of time. Bacterial and fungal susceptibility was explored in field studies on isolates taken between day 0 and day 28. Post treatment MICs remained within the range observed in other clinical studies and described in literature, and a resistance pattern was not identified. It is seen that there is a theoretical risk in exposing "new" colonizing bacteria and fungi in the external ear to sub-MIC concentrations of antimicrobial agents and in this regard advice has been added to the product literature concerning correct timing of resuming ear cleaning practices after the effective treatment period.

Pharmacokinetics

The applicant has provided bibliographic references on the pharmacokinetic properties of florfenicol and terbinafine. No information regarding the pharmacokinetics of mometasone furoate following topical application in dogs has been found in literature search.

The applicant has conducted two PK studies: one pilot study and a pivotal GLP-compliant study conducted following the scientific advice provided by the CVMP. The main conclusion of this research is that some systemic absorption takes place, although low levels of the three compounds were

detected in plasma compared with the concentrations found in the ears.

Dose determination

The dose of Neptra was established based on findings of five dose determination studies (four pilot field studies and one dose determination field study).

Even though the recalculated results from two pilot studies failed to show superiority of the IVP compared to placebo, the overall data is supportive for the chosen formulation and dose. Therefore, when the results of the pilot studies and the dose determination study are taken into consideration, the choice of the formulation and dose is acceptable.

Tolerance

Neptra was well-tolerated in a series of laboratory and field studies at the recommended dose of 1 ml containing 16.7 mg florfenicol, 16.7 mg terbinafine hydrochloride and 2.2 mg mometasone furoate.

In the pivotal TAS study, no product-related findings were noted at physical examinations or hearing tests other than wet ears/clear discharge in animals given 1X the RTD, and variably on Days 1, 15, and/or 29 in all animals given 3X or 5X the RTD. The main findings seen at the 1X the RTD (decreases in cortical response to ACTH stimulation, decreased absolute lymphocyte and eosinophil counts, and decreased adrenal weight) and at 3X and 5X the RTD (increased neutrophil counts [5X males only], increased cholesterol) were due to the glucocorticoid substance.

Based on literature data and the results from the pivotal TAS study, it is accepted that recovery from HPA axis suppression caused by treatment with Neptra would be seen within 1-2 weeks after treatment.

Based on the data provided, it is concluded that the product is generally well-tolerated at the recommended dose. However, all the adverse events recorded in the studies are captured in the SPC, as well as the adverse events with a probable or possible causality reported for the identical product marketed in the USA (Claro).

Efficacy

The results from three clinical field trials show that the product is efficacious for the treatment of acute canine otitis externa or acute exacerbations of recurrent otitis caused by mixed infections of susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*) at the proposed dose of 1 ml containing 16.7 mg florfenicol, 16.7 mg terbinafine hydrochloride and 2.2 mg mometasone furoate in dogs.

Part 5 – Benefit-risk assessment

Introduction

Neptra ear drops contain a fixed combination of 3 active substances: florfenicol / terbinafine hydrochloride / mometasone furoate. The combination has not been previously authorised within the EU.

The active substances of Neptra are florfenicol, an antibacterial, terbinafine hydrochloride, an antifungal and mometasone furoate, a corticosteroid which reduces inflammation of the skin. The target species is dogs.

The proposed dose is 1 ml (one tube) per infected ear.

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 applicant submitted on 10 July 2018 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Neptra, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The application has been submitted in accordance with Article 13b of Directive 2001/82/EC – a fixed combination application.

Benefit assessment

Direct therapeutic benefit

Neptra is a fixed combination of the antibiotic florfenicol, the antifungal terbinafine HCl and the glucocorticoid mometasone furoate. It is intended for treatment of canine otitis externa caused by mixed infections of susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*). Combinations of active substance classes with antibacterial, antifungal and anti-inflammatory activity are established treatment principles for the treatment of external ear infections in dogs. The combination of florfenicol, terbinafine hydrochloride and mometasone furoate in an ear drop solution is justified based on the fact that the disease is multi-factorial and treatment success generally requires antibacterial, antifungal and anti-inflammatory efficacy. The justification for the fixed combination product has been strengthened by refining the indication of use to address only mixed infections, where both target pathogens have been demonstrated.

The applicant submitted 2 pivotal field trials in order to demonstrate the efficacy of Neptra for the treatment of canine otitis externa caused by mixed infections of susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*). According to the results, the efficacy of the product is demonstrated when used according to the SPC.

Additional benefits

It can be accepted that the single-administration dosage regimen is an additional benefit because of the reduced manipulation of the dog ear and better owner compliance.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and finished product has been presented. The results of tests carried out indicate consistency and uniformity of important product quality characteristics.

Safety:

Risks for the target animal:

Concerns have been raised for eye irritancy based on preclinical studies. Administration of Neptra in accordance with SPC recommendations is generally well-tolerated. The safety of florfenicol / terbinafine hydrochloride / mometasone furoate in dogs was confirmed in two target animal safety studies and in several laboratory and field studies. In the pivotal TAS study, no Neptra-related

findings were noted at physical examinations or hearing tests other than wet ears/clear discharge seen in animals given 1X, and variably on Days 1, 15, and/or 29 in all animals given 3X or 5X the RTD. The main findings seen at all dose levels were a statistically significant decrease in cortical response to ACTH stimulation, decreased absolute lymphocyte and eosinophil counts, and decreased adrenal weight, which were due to the glucocorticoid substance. Suppression of the hypothalamic-pituitary-adrenal (HPA) axis was not studied in the field studies and reversibility of the suppression of the HPA axis was not studied at all. However, the applicant provided literature on the expected recovery from the HPA axis suppression and it was concluded that the suppression caused by this product is comparable to other similar products and that the proposed risk mitigation measures (SPC warnings) are sufficient to control the issue.

Adverse events reported in the field studies were all considered as not treatment related. However, as Neptra is identical to a product authorised in the USA (Claro), the applicant provided a summary of the adverse reactions with A- or B-causality in the PSURs for Claro and these were added to the product literature.

Risk for the user:

Neptra may have serious eye irritating potential; ocular exposure represents a relevant risk for local effects. No risk is envisaged for pregnant women and women with childbearing potential as a result of use of Neptra whereas risk cannot be ruled out for children and adults during contact with the treated dog. Accordingly, risk management and risk communication measures are proposed.

Risk for the environment:

Neptra is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Special risks:

Concerns have been raised relating to the potential for resistance emergence and in this regard aspects relating to the long acting formulation such as the risk of AMR due to long sub-MIC concentrations of the antimicrobial active ingredients were discussed. It is considered that these concerns have been appropriately addressed by the addition of advice and warnings in the product information.

Risk management or mitigation measures

User safety:

Risk management measures are proposed to address the local adverse effects of Neptra and the potential risks for children and adults during contact with the treated dog.

Antimicrobial resistance:

Neptra is a combination of three active substances, which has not been used in veterinary medicine before. The risk of resistance development with regard to the use of this product can be considered low, but to mitigate the possible risk pertaining to sub-MIC concentrations of antimicrobials, advice on the correct timing of ear cleaning after the treatment has been added in the product information (in addition to standard warnings concerning use of antimicrobials).

Evaluation of the benefit-risk balance

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

The product indication as initially proposed by the applicant was "For the treatment of canine otitis externa caused by susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis)*". Following evaluation of the data, the CVMP agreed to the following indication(s): Treatment of canine otitis externa caused by mixed infections of susceptible strains of bacteria sensitive to florfenicol (*Staphylococcus pseudintermedius*) and fungi sensitive to terbinafine (*Malassezia pachydermatis*).

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, the environment and consumers, when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Neptra 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.