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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for granting of marketing authorisation for OSURNIA (EMEA/V/C/003753/0000)

International non-proprietary name: terbinafine, florfenicol and betamethasone

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

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Introduction

On 26 June 2013, the applicant Novartis Santé Animale S.A.S. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for OSURNIA ear gel for dogs, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (new active substance).

The eligibility to the centralised procedure was agreed upon by the CVMP on 7 February 2013 as OSURNIA contains a new fixed combination of active substances florfenicol, betamethasone acetate and terbinafine which was not authorised in the European Union (EU) on the date of entry into force of the Regulation. In addition, terbinafine is a new active substance. The rapporteur appointed was M. Holzhauser-Alberti and the co-rapporteur was E. Lander Persson.

The proposed indication is: Treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*. The target species is dogs. OSURNIA is presented in packs/containers of 2, 12, 20 or 40 tubes. The product is intended for auricular use.

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

On 5 June 2014 the CVMP adopted an opinion and CVMP assessment report.

On 31 July 2014 the European Commission adopted a Commission Decision for this application.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the Novartis pharmacovigilance system (version 2.3) has been provided.

A statement signed by the applicant and the qualified person for pharmacovigilance has been provided stating that the applicant has the services of a qualified person for pharmacovigilance. The Novartis pharmacovigilance system described fulfils the requirements and shows the applicant has the necessary means for the notification of any adverse reaction suspected of occurring either in the European Union (EU) or in a third country.

Manufacturing authorisations and inspection status

Active substances

OSURNIA contains three active substances, florfenicol, betamethasone acetate and terbinafine. A declaration of the compliance of the manufacture of all the active substances with EU good manufacturing practice (GMP) requirements for starting materials has been provided from the qualified person at the batch release site.

Finished product

The finished product manufacturer, Vericore, is located in the UK and was inspected by the Veterinary Medicines Directorate, UK, in June 2012. GMP certification is available for the site which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms.

Batch testing is performed at the same Vericore site, but also at UFAG Laboratorien AG in Switzerland, for which GMP compliance was confirmed by the competent national authority (Swissmedic) in January 2012.

Overall conclusions on administrative particulars

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

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

Part 2 – Quality

Composition

The finished product, OSURNIA ear gel for dogs, contains terbinafine, florfenicol and betamethasone acetate as active substances. Each single dose 1.2 g tube contains 10 mg, 10 mg and 1 mg of the three active substances, respectively.

The excipients included in the gel formulation are: butylhydroxytoluene (antioxidant), oleic acid (counter ion), lecithin (for viscosity adjustment), hypromellose (for viscosity adjustment), propylene carbonate (solvent), and glycerol formal (solvent) (which is itself stabilized with butylhydroxytoluene).

Container

The gel is packaged in unit-dose tubes, each with a flexible polypropylene/elastomer applicator tip. The tube is composed of 2 parts: the body (with multilayers made of aluminium and polyethylene (HDPE and LDPE)) and the shoulders (HDPE). Full details have been provided. The container plays an important role in controlling the viscosity of the gel, during both storage and also during administration into the ear(s) of the target animal. The applicant has studied several types of packaging and it has been demonstrated that the proposed packaging is the most appropriate for this product in terms of minimizing product-container interactions and optimizing the efficiency of product administration.

Development pharmaceutics

The objective of the pharmaceutical development program for OSURNIA ear gel for dogs was to develop a unit-dose product to treat dogs' ear infections with sufficient efficacy after only one or two applications.

Also taken into consideration during development was the highly hydrophobic environment of the ear, and the formulation was developed accordingly. The product contains both classical excipients for such a gel formulation, and also some excipients (lecithin and hypromellose) which confer onto the product specific physico-chemical characteristics, defined by the applicant as "pseudoplastic". These characteristics allow the product to persist for several days within the ear canal of treated dogs after administration. The choice of the active substances and excipients included in the formulation is considered as fully justified.

As the product is packaged into single-dose tubes, the absence of a preservative is justified.

Data have also been provided on the homogeneity of the gel in the tubes.

Method of manufacture

The manufacturing process is a standard method involving adding and dissolving/dispersing solids in the vehicle, which is then filled into the primary containers (unit-dose tubes). The manufacturing process starts with the dissolution of the active substances with some excipients. The gel is formed in the last step after addition of glycerol formal (under heat).

No overages are used.

The applicant has provided adequate details of the manufacturing process and in-process controls.

No process validation studies have yet been undertaken at the industrial scale; however the manufacturing process is accepted to be a standard one. The applicant is therefore recommended to perform process validation studies, according to the validation protocol provided, on three full scale batches before commercialisation.

Control of starting materials

Active substances

The finished product contains three active substances: betamethasone acetate which is described in the European Pharmacopoeia (Ph. Eur.), and terbinafine and florfenicol which are not described in the Ph. Eur.

For the control and manufacture of the active substances betamethasone acetate and florfenicol, data are provided in the form of active substance master files (ASMFs). For the control and manufacture of the active substance terbinafine, full data are provided in the application. The active substance specifications include tests and limits for residual solvents which are in compliance with International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) GL18 (Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients). The specifications also include tests and limits for impurities in accordance with VICH GL10 (Impurities in new veterinary drug substances). The assays for florfenicol and betamethasone are performed by high-performance liquid chromatography (HPLC), and for terbinafine by titration. Other tests such as for impurities, melting point, loss on drying, pH, etc., are included in the specifications of the active substances and are considered appropriate for their control.

All the analytical methods have been sufficiently well described and appropriately validated.

Results of VICH-conforming stability studies have been presented which justify the claimed retest periods of 5 years for the betamethasone acetate and the terbinafine, and 3 years for the florfenicol.

Excipients

Butylhydroxytoluene, oleic acid and hypromellose are controlled according to the requirements of the respective Ph. Eur. monographs. Propylene carbonate is described in the United States Pharmacopeia and the National Formulary (USP/NF).

Glycerol formal is purchased stabilized with butylhydroxytoluene and tested according to an in-house monograph. The glycerol formal and butylhydroxytoluene are controlled separately according to their respective Ph. Eur. monographs.

Lecithin is tested according to an in-house monograph based on the USP/NF monograph with some additional tests to ensure a more suitable quality of the excipient for this particular product. The additional tests have been justified and appropriately validated.

All the specifications and certificates of analysis provided comply with the relevant requirements.

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

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

The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The proposed release specification is acceptable for this type of dosage form even though not all release specifications were tested in accordance with VICH GL39 (Test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances) since this guideline is not mandatory for gel formulations. This was considered acceptable by the CVMP.

The analytical methods used for the control of the finished product (appearance, viscosity, pH, water content, identity, assay, uniformity of dosage units, related substances, residual solvents and microbial quality) are sufficiently well described.

The shelf life specification is different from the release specification only with regard to uniformity of dosage units, identification and limits for assay and related substances, but the differences are justified.

All the analytical test methods are adequately validated.

Results of the analysis of three production batches of finished product, which demonstrate compliance with the required specification, are presented.

Stability

The limits in the shelf life specification have been established based on the stability data obtained from 3 industrial batches and this has been justified.

As the primary packaging is totally opaque no photostability data has been provided for the finished product, and this is acceptable.

The shelf life specification includes tests and limits for residual solvents which are in compliance with the VICH GL18, tests and limits for impurities in accordance with the VICH GL10, and also appropriate microbial tests. The limits for assay of each of the active substances are set at 90–105% of the theoretical values and are justified.

Stability studies have been performed on three commercial scale batches. The results are available after storage of the product for up to 24 months at 5 °C, 25 °C/60% relative humidity (RH), 30 °C/65% RH and up to 9 months at 40 °C/75% RH (i.e. VICH conditions). A shelf life of 2 years with the storage precaution “Store in a refrigerator (2 °C – 8 °C)” is proposed by the applicant and this has been sufficiently justified by the data provided.

The applicant did propose a shelf life of 3 months without any special temperature storage condition after removal of the product from the refrigerator; however, in order to avoid confusion over storage of the product the CVMP agreed that these instructions should not be included in sections 6.3 and 6.4 of the summary of product characteristics (SPC).

Overall conclusions on quality

The rationale for the choice of the formulation is acceptable.

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

The data for two of the active substances (betamethasone acetate and florfenicol) is presented in an ASMF. Each includes comprehensive information on the starting materials, manufacture, characteristics and control of the relevant active substance. The data for the terbinafine is provided in the dossier. Only the betamethasone acetate is the subject of a Ph. Eur. monograph. Neither of the other two actives are the subject of a monograph of the Ph. Eur. or a pharmacopoeia of any EU Member State and therefore both are tested in accordance with in-house monographs, which are satisfactory.

The excipients are all the subject of appropriate specifications.

Appropriate information is provided for the packaging materials for the unit-dose tubes for this ear gel.

There are no concerns in relation to TSE for any of the ingredients of the product.

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

Suitable stability studies according to VICH guidelines have been carried out and the data provided support the shelf life of 2 years when stored in a refrigerator (2 °C – 8 °C).

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

Part 3 – Safety

Safety documentation

OSURNIA is a combination of three active substances – florfenicol, betamethasone acetate and terbinafine. Terbinafine has been used in human medicine for several decades but is a new substance in a veterinary medicinal product. Florfenicol and betamethasone are already present in veterinary medicinal products, but florfenicol is not used in a veterinary product intended for dogs.

Pharmacodynamics

See Part 4.

Pharmacokinetics

See Part 4.

Toxicological studies

The toxicological profiles of florfenicol and betamethasone were assessed by the CVMP during maximum residue limits (MRL) procedures for these substances and are described in the published Summary Reports. The available toxicological data regarding betamethasone did not concern the acetate salt, but the free alcohol or valerate salt. However, the toxicological profile of betamethasone acetate should not significantly differ from alcohol or other salt forms. In addition to the information from the MRL summary reports regarding florfenicol and betamethasone (1996 and 1999), and the applicant provided more recent information based on a literature search for pharmacodynamics, pharmacokinetics and toxicology information for florfenicol and betamethasone in all species, which confirmed that the provided toxicological profiles for florfenicol and betamethasone in laboratory animals remained unchanged.

The toxicological data on terbinafine were new for veterinary medicinal product application, but have been reviewed for human medicinal product applications already.

Single dose toxicity

Acute toxicity of the 3 active substances is low. After oral or dermal exposure in rats, the acute toxicity of the test product is also low (LD_{50} > 2,000 mg/kg).

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). 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 overall acceptable daily intake (ADI) of 0.010 mg/kg (600 µg/person) was established from this NOEL.

Betamethasone was tested in rats (studies ranging from 28 days to 9 months), dogs (studies ranging from 6 days to 6 weeks) and monkeys (12 months). Effects seen in rats were reduced bodyweight, changes in haematological parameters, and thymic and adrenal atrophy. Effects in dogs included muscular wasting, pot-belliedness and polydipsia, haematological changes, adrenal and thymus atrophy, increased liver weights associated with increased glycogen content. Effects in monkeys included reduced bodyweight gain, haematological changes, and adrenal and lymphoid atrophy. For betamethasone, the most appropriate NOEL for the establishment of the overall ADI was not considered to be a toxicological one, but a pharmacological NOEL of 0.004 mg/kg was established based on increase of tyrosine aminotransferase activity in rat liver. An ADI of 0.000015 mg/kg (0.0009 mg/person) was retained, which is the same as the ADI established for the similar substance dexamethasone.

After oral administration of terbinafine to mice, rats or dogs the main target organ was the liver (hepatomegaly, increased activity of hepatic enzymes and in rats, proliferation of hepatic peroxisomes). The lowest oral NOEL was 25 mg/kg from a 52-weeks toxicity study in dogs (based on clinical signs and increase of hepatic P450 activity). In monkeys a reversible ocular toxicity was observed (refractile bodies in the retina) after oral repeated administrations of 150 or 300 mg/kg terbinafine/day for 32 weeks, a NOEL of 20 mg/kg/day was retained from this study. After daily dermal application in rabbits for 4 weeks or 26 weeks of cream or solution formulation of terbinafine, no systemic signs were observed, but local reactions were recorded in all treated animals. The severity was not dose-related. No dermal NOEL was established. After vaginal application of 150 mg/kg terbinafine/day for 14 days in beagle dogs, no local or systemic effects were observed.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Florfenicol did not induce embryo/foetotoxicity or teratogenicity.

As other corticosteroids, betamethasone possesses embryotoxic and teratogenic properties. Developmental toxicity has been investigated in rabbits, rats and mice. The lowest NOEL for teratogenicity was 0.003 mg/kg, retained from a subcutaneous teratogenicity study in rabbits. In view of the known teratogenic effects in laboratory animals, and the absence of such safety data in the target species, the use of the product is contraindicated in pregnant and lactating bitches.

For terbinafine, in a developmental toxicity study rats were orally administered with 10, 50 or 250 mg/kg/day with terbinafine before mating, and during pregnancy and lactation. Embryotoxicity was observed at maternotoxic doses only. From this study a NOEL for maternotoxicity and embryotoxicity of 50 mg/kg was established from a study in rats. Terbinafine showed no potential for teratogenicity in rats and rabbits.

Mutagenicity / genotoxicity

The three active substances were devoid of mutagenic/genotoxic potential in a battery of suitable genotoxic tests (florfenicol: *in vitro* tests for gene mutation in bacterial and mammalian cells systems, *in vivo* micronucleus test and chromosome aberrations test in bone marrow; terbinafine: 2 Ames tests, an *in vitro* test on V79 Chinese hamster cells, an unscheduled DNA synthesis (UDS) test on rat hepatocyte primary cells and an *in vivo* micronucleus test; betamethasone: Ames tests in *Salmonella typhimurium* and *Escherichia coli*, an *in vitro* forward point mutation assay (HPRT locus) in Chinese hamster ovary (CHO) cells, an *in vitro* chromosomal aberration assay in human lymphocytes, an *in vivo* micronucleus test).

Carcinogenicity

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

Betamethasone was not tested in carcinogenicity studies but based on the negative results in genotoxicity tests and based on the absence of carcinogenicity findings for similar substances, the substance is considered to be devoid of carcinogenic potential.

In mice, terbinafine was shown to be non-carcinogenic. In a carcinogenicity study in rats, the highest dose (69 mg/kg for 123 weeks) produced a small, but statistically significant, increase in the incidence of hepatocellular tumours in male rats. The changes which may be associated with peroxisome proliferation have been shown to be species-specific since they were not seen in the carcinogenicity study in mice or dogs, and terbinafine is not expected to have carcinogenic potential in human and dogs.

Studies of other effects

Based on old, but well conducted, skin irritation, ocular irritation studies, and in a skin sensitization test, terbinafine was considered as a non-skin irritant, a non-eye irritant and a non-skin sensitising agent.

For the other active substances florfenicol and betamethasone, no specific studies were submitted, in which skin irritant, eye irritant or skin sensitising potential were tested. However, it was noted that in none of the general toxicity studies with these substances, any irritant or sensitising effects were reported at any time.

In well conducted recent studies, the final product containing all three active substances was found to be non-irritant to the rabbit's skin, to be moderately irritant for rabbit's eyes, and was not a skin sensitizer in local lymph nodes of female mice.

User safety

The applicant has presented a User Safety Risk Assessment which has been broadly conducted in accordance with CVMP guideline EMEA/CVMP/543/03-Rev.1. The product is an ear gel, with florfenicol, betamethasone acetate and terbinafine as active ingredients. Excipients of the product are currently used in veterinary and human medicine and do not raise any toxicological concern. The product is presented as a tube, and administered twice, at 7-days interval. It is expected that the product will initially be administered by a professional user (veterinarian or under his/her direct responsibility), but the second dose might be administered by the dog's owner; the product might therefore also be stored in the animal owner's household.

User exposure may be oral, dermal or ocular.

For dermal exposure, margins of exposure were calculated, taking into account that the type and the level of exposure are of low probability. Furthermore, the product was shown to be non-skin irritant and with very low dermal acute toxicity.

For ocular exposure, considering the very low quantity of product that might reach the eyes, the risk after ocular contact was considered to be low, even if the product was shown to be moderately irritant to the eyes. Furthermore, a relevant warning has been included in the SPC regarding ocular contact.

After oral exposure, taking into account the very low acute toxicity of the product, the risk in case of ingestion appeared to be very low. In the case of accidental ingestion of 100% of the total dose (worst case scenario) by a 10-kg child, the margin of safety would only be lower than 1 for betamethasone, and there could be a potential risk. However, it is unlikely that a child would ingest the whole content of a tube and only a fraction of the total quantity might be ingested. Even with exposure of 20% margins are too low (except for terbinafine). However, it could be argued that the NOEL value/safe levels were derived from repeated exposure, and accidental ingestion by a child is probably a single event, also the effects are not life-threatening making it possible to accept a lower margin. In any case appropriate risk mitigation measures should be applied. The conclusions were in line with those for other ear gels regarding the glucocorticosteroid component. It should also be pointed out that because of the packaging, a 10-kg child (approximately 2 years of age) should not be viewed as capable of easily opening the tube. The CVMP also noted that a child may be in contact with a treated dog when the animal comes back home. Nevertheless, the level of oral exposure would be negligible and, taking into account the low acute oral toxicity of the product, the risk for a child was considered to be negligible.

The risk for embryos/foetuses of pregnant women due to the betamethasone component of the combination was not specifically addressed by the applicant. However, based on the lowest NOEL for teratogenic effects of betamethasone in rabbits (0.003 mg/kg following subcutaneous administration) the calculated margin between the estimated systemic betamethasone exposure of 0.003 mg/kg in humans following dermal exposure and 0.003 mg/kg (in case of 100% absorption) following a subcutaneous dose in rabbits at which no teratogenic effects were observed, would be around 1. Following oral exposure, the calculated margin for teratogenic effects (up to 2 x 0.003 mg/kg following oral administration based on

the study in rabbits versus the estimated oral exposure of 0.006 mg/kg in humans following hand to mouth exposure) would be around 1 as well. However, the risk for pregnant women was considered to be appropriately addressed by the user safety warning to wash hands. In addition, the probability and the extent of dermal or oral exposure of pregnant women are considered to be low. Thus, the lack of, or a low exposure margin with respect to teratogenic effects of betamethasone was accepted.

The CVMP considered therefore that the proposed warning sentences in the SPC were adequate to ensure the safety of the user, including a child, if the product is used as recommended.

Environmental risk assessment

A Phase I environmental risk assessment was provided in line with line with the VICH GL6 (Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I) (CVMP/VICH/592/98-FINAL). Given that the product is for the treatment of dogs, the environmental risk assessment can stop at Phase I.

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

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 had no potential for embryo/foetotoxicity or teratogenicity. For terbinafine, a NOEL for maternotoxicity and embryotoxicity of 50 mg/kg was established from a study in rats, and terbinafine had no potential for teratogenicity. However, as other corticosteroids, betamethasone possesses embryotoxic and teratogenic properties, and a contraindication for use in pregnant animals has therefore been included in the product information.

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

Florfenicol and betamethasone are considered to be devoid of carcinogenic potential. Although terbinafine induced hepatic tumour in rats (but not in mice), negative results were obtained in genotoxicity tests, indicating that terbinafine may be acting as a non-genotoxic carcinogen in male rats. It was established that the mechanism of such carcinogenicity was due to peroxisome proliferation. This observation was made only in rats and not in humans and consequently the tumorigenic action seen in rats is not considered relevant for humans or dogs.

The test product was shown to be non-irritant to skin, a moderate ocular irritant and a non-sensitizer of skin in recent well conducted studies.

A user risk assessment was provided, and it was concluded that the current warnings in the SPC are sufficient to ensure the safety of the user, including a child, if the product is used as recommended. If used as recommended, the product will have a negligible impact on the environment.

In conclusion, the provided toxicological data were sufficient to conclude on the toxicological profile of the product. If used as recommended, the product does not pose an unacceptable risk to the user and to the environment.

Residues documentation

Not applicable.

Part 4 – Efficacy

Justification of the fixed combination

OSURNIA contains three active substances, an antibiotic, an anti-fungal and a glucocorticosteroid. The applicant justified the combination by the need to cover a broad antibacterial and antifungal spectrum to treat otitis associated with bacteria and fungi. Furthermore, a non-good laboratory practice (GLP) study using a model of murine skin inflammation was conducted in order to investigate the suitability of betamethasone as the anti-inflammatory component of the product. Clinical field trials confirm that otitis externa in dogs may be associated with Gram-positive bacteria (mainly *S. pseudintermedius*), Gram-negative bacteria (*E. coli, Proteus* spp*., Pseudomonas* spp.) and/or yeasts (*M. pachydermatis*).

Negative interactions between the active substances in the product were studied and did not appear to be of any significance.

Pharmacodynamics

OSURNIA contains three active substances: florfenicol, terbinafine, and betamethasone acetate.

Florfenicol is a fluorinated analogue of chloramphenicol acting on the protein synthesis of bacteria, and is primarily considered to be a bacteriostatic drug that stops bacterial growth by inhibiting protein synthesis. Susceptibility of the different target pathogens isolated in ears of dogs in Europe and United States of America (USA) were provided. The following minimum inhibitory concentrations (MIC_{90}) were determined in Europe: 16 µg/ml for *E. coli*, 8 µg/ml for *Staphylococcus pseudintermedius*, *Staphylococcus* spp*.* non-*intermedius, Proteus* spp*.* and *Enterococcus* spp., and 2 to >128 µg/ml for *Streptococcus* spp. Florfenicol has very limited activity against *Pseudomonas* species with MIC_{90} 1,024 µg/ml. Resistance could be conferred by notably two mechanisms, the efflux pump resistance associated with a *floR* gene and the *Cfr* rRNA methyltransferase associated with a *Cfr* gene. This last mechanism confers resistance to phenicols, lincosamides, oxazolidinones, pleuromutilins, and streptogramin A antibiotics. These two genes are located on plasmids.

Terbinafine is an allylamine which specifically inhibits fungal ergosterol biosynthesis at the point of squalene epoxidation. As a result of this inhibition by terbinafine, the treated fungal cells rapidly accumulate the intermediate squalene and become deficient in the end-product of the pathway, ergosterol. Terbinafine has fungicidal activity against *Malassezia pachydermatis* with MIC_{90} of 2 µg/ml. Allylamine resistance may be mediated through mutations in Erg1p, efflux via ABC transporters, stress tolerance induction, or induction of detoxification.

Betamethasone acetate is a glucocorticosteroid and has anti-inflammatory action.

An *in vitro* non-interference (MIC) study of combinations of florfenicol, terbinafine and betamethasone acetate against bacterial and yeast isolates was provided. In general no interference was found which is expected because of the different modes of action.

Development of resistance

For terbinafine, the MIC distribution of *M. pachydermatis* is modal and hence the likelihood of a subpopulation that is resistant was low.

For florfenicol, however, the MIC distribution showed some sub-population with decreased susceptibility for some target pathogens isolated from clinical cases of otitis externa in the field clinical studies:

MIC ranged from 1 to >64 µg/ml for *E. coli,* from 0.25 to 32 µg/ml for *S. pseudintermedius,* from 2 to 32 µg/ml for *Staphylococcus* spp. non-*intermedius,* from 0.5 to >128 µg/ml for *Streptococcus* spp., from 4 to 16 µg/ml for *Proteus* spp.*,* from 1 to 8 µg/ml for *Enterococcus* spp., and >64 µg/ml for *Pseudomonas* spp.

No resistant organism was observed after treatment with OSURNIA. The applicant has discussed the possible risk of the antimicrobial resistance transfer from companion animals to people, as this product is the first use of florfenicol in dogs. The applicant did not exclude the risk of development of resistance and the co-selection for resistance for several classes of antimicrobials, also, a transfer of antimicrobial resistance from dogs to humans might be possible. However, the applicant considered that the local concentration after each of two applications would be hundreds or thousands times higher than after a systemic administration, indicating a low probability of any antimicrobial resistance for several classes of antibiotics. The applicant also considered that antimicrobial resistance to florfenicol or co-selection for resistance for several classes of antibiotics would not be clinically relevant to humans or companion animals, given the long term use of florfenicol in veterinary medicine, where benefits still outweigh risks.

The CVMP agreed with the applicant's conclusions, and considered that the risk of resistance development and spread for florfenicol, although in principle possible for such a product where the animal is in close contact with the owner, seemed unlikely and not highly critical for this ear gel product used in individual companion animals since local concentrations of florfenicol were very high for a sufficiently long period of time.

Pharmacokinetics

Pilot and pivotal GLP or non-GLP ear and plasmatic pharmacokinetic studies in dog after auricular application were provided. Different volumes of administration or different concentrations of florfenicol in the formulation have been assessed.

After administration of the product, as recommended, concentrations of florfenicol and terbinafine in the ear canal of healthy dogs were largely higher than the MIC of susceptible target pathogens.

Seven days after the first administration, mean concentrations of betamethasone acetate, florfenicol and terbinafine were 615 ng/mg, 7,998.9 ng/mg and 5,870.5 ng/mg, respectively; and 7 days after the second administration, mean concentrations were 910 ng/mg, 11,794.2 ng/mg and 7,346.4 ng/mg, respectively. This suggests that there was little or no accumulation after the second administration one week later. Elimination half-lives in ears were around 4–5 days.

Systemic absorption of the three active substances was of the magnitude of ng/ml, and likely to occur over 2–4 days after administration. It was noted that no cleaning of the ear was proposed after treatment has been initiated. Hence, this aspect of pharmacokinetics was important to consider especially for the absorption of betamethasone, which could, at these doses, potentially lead to some adverse effects systemically (see also tolerance section regarding betamethasone).

Dose determination / justification

Antifungal and antibacterial components: in the ear swabs from experimental studies, the concentrations of florfenicol and terbinafine were much higher than the MICs of the target organisms. These concentrations were several hundred times the MICs of pathogens for both florfenicol and terbinafine. The applicant also demonstrated that the formulation persists in the ear canal for several weeks at concentrations exceeding the MICs by several hundred multiples. However, in clinical cases of otitis externa, organisms may be protected from the antibiotics by a biofilm, and the concentrations of

antibiotic required to inhibit the growth of the bacteria is unknown. The applicant's dose justification was not considered to be fully robust, but it was generally accepted that local concentrations of the active substances in the ear are, and might need to be, much higher than the MICs of the target organisms. A pharmacokinetic-pharmacodynamic model (PK-PD) was not considered helpful for determining the dose, which the CVMP accepted for this type of product.

The dose justification of the glucocorticosteroid was based not only on the efficacy aspects, but on the tolerance aspects. Some absorption in the treated dog's ear of betamethasone has been demonstrated, leading to detectable systemic concentrations. At the chosen concentration of betamethasone in the formulation (1 mg), these reversible systemic concentrations lead to no clinical side-effects in treated dogs (see also tolerance section).

In order to justify the repeated administration, the applicant submitted two field studies undertaken in Europe (INT-09-001) and USA (NAH-09-0006) using a single dose of OSURNIA compared to a positive control (EU study) or a placebo (USA study). Both studies were randomized, blinded, multicentre and performed under good clinical practice (GCP). The clinical response was assessed on days 14, 28 and 60 in the EU study, and on days 7, 30 and 45 in the USA study. In both studies, an insufficient efficacy of the tested formulation was found after a single administration. In the EU study, the bacteriological culture and the cytology scores were higher on day 14 in the OSURNIA group compared to the control product, suggesting insufficient control of infection. Based on the results of the field clinical and the ear swab studies, the applicant selected a repeated dose of OSURNIA (containing 10 mg terbinafine, 10 mg florfenicol and 1 mg betamethasone) to be administered twice (the second dose given after 7 days) to be tested in the field trials, which showed consistently high efficacy.

Target animal tolerance

Two non-pivotal and one pivotal tolerance study were performed. They were conducted with the final formulation on healthy mongrel dogs (without auricular lesions).

In the first non-pivotal GLP study (NAH-10-0014, 2012; Wisconsin, USA), healthy dogs received placebo, 1X, 3X or 5X the recommended dose (up to 10 ml/ear) (4 animals/sex/group). The product was administered 3 times, 7 days apart (instead of 2 times, 7 days apart as proposed in the SPC).

After 3 weekly administrations of up to 5X the recommended posology, treated dogs showed no clinical signs and no hearing disturbances, though the study details on what was included in the clinical examination were not given. Only wet ears and white discharge were noted. As there were neither associated clinical signs nor histological findings, these observations were concluded to have no toxicological significance. They were due to the physical presence of the gel.

Significant findings concerned a decrease of cortisol levels and a reduced response to adrenocorticotropic hormone (ACTH) stimulation at all tested doses. Cortisol values remained within the normal reference range of 6–17 µg/dl in 1X dosed group, but were significantly below this range in the 3X and 5X dosed groups. These findings were associated with decreased adrenal, splenic and thymic weights, and histological adaptive atrophy of the adrenocortical. A lymphocyte depletion was noted in all treated males and only in 5X dosed females. Incidence and severity of these findings were dose-related. However, these findings were not accompanied by clinical signs. These observations were linked to pharmacologic properties of betamethasone. Although this study was non-pivotal, the observations confirmed that betamethasone was absorbed in a sufficient quantity to have effects on systemic cortisol levels, even after instillations of the recommended dose.

The second non-pivotal non-GLP study (YAR-11-036, 2012; Australia) was performed to examine effects of the product on the adrenal glands following auricular administrations, using three groups of 2 animals

per sex each. Dogs received 3 ml/ear three times, one week apart, 1 ml/ear six times one week and two weeks apart. The test item was applied via direct topical application intra auricular. An ACTH stimulation test was performed once on all dogs on D-7 (pre-treatment values) and then at fixed time points for each group.

No effects on hearing and no toxic signs were observed up to 3 times the recommended dose administered in excess compared to the recommended duration. Dose-dependent decreased cortisol levels were observed in all treatment groups after product's instillation (before and after ACTH stimulation). This finding was not correlated with pathological or clinical signs and it was reversible. Again, this study showed that betamethasone acetate was absorbed systematically sufficiently to induce reversible effects on systemic cortisol levels, even at the recommended posology.

In the well conducted GLP pivotal tolerance study (GSO-12-002, 2013; Maryland, USA), that followed requirements of VICH target animal safety guideline, 24 healthy mongrel dogs aged 3–4 months received 0, 1X or 5X the recommended dose of product (4 animals/sex/group). The product was instilled into both ear canals on D1, D8, D15, D22, D29 and D36, i.e. 3 times the recommended "duration" (twice at 7 days interval).

In both treated groups, the bodyweight gain was lower than in the untreated control group. This observation was consistent with the known effects of corticosteroids. In the field, the administration of five times the recommended dose of this unidose packaged product is very unlikely to occur. In addition, the effects are reversible in all dogs.

Ear wetness was noted in both treated groups. This was associated to the presence of the formulation rather than pharmacological effect caused by the active substances. No hearing disturbances were detected.

Slight to moderate unilateral vesicle blister formation within the epithelium of the tympanic membrane was also noted in 2 females after 6 administrations of 1 ml of the product per ear. These lesions were visible upon microscopic ear examination, but did not manifest themselves clinically. Both affected female dogs had normal hearing and remained healthy. The blistering in the epithelium of the tympanic membrane is reversible, and considered to occur through epithelial migration, a natural self-cleaning process for the tympanic membrane and ear canal, and known self-repair mechanisms for the tympanic membrane in the dog (N. E. Tabacca et al., in Veterinary Dermatology, 2011, Vol. 22(6), p. 502–510).

Dogs receiving 5X the recommended dosage showed unilateral ulceration of the lining of the middle ear cavity and slight haematological and biochemical changes (elevated red blood cells (RBC), haematocrit (HCT), total protein, albumin and alanine aminotransferase (ALT)). Regarding ulceration of the lining of the middle ear cavity at 5 times the recommended dosage, a tympanic membrane damage might have occurred by chemical irritation following multiple applications of large volumes rather than by mechanical disruption, leading to inadvertent local entrance of the product into the middle ear cavity. It suggested that, in case of overdose, the product might have irritating properties. However, an overdose of this unit-dose packaged product would be very unlikely.

In both treated groups, a decrease in cortisol level after ACTH stimulation was noted. It was consistent with known pharmacologic properties of betamethasone as a corticosteroid. At the recommended dose, this observation was not associated with any pathological finding. But at 5X the recommended dose, correlated findings were decreased adrenal gland and thymic weights with microscopic correlates of minimal adrenal cortical atrophy in all dogs, and mild/moderate lymphoid depletion of the thymus in three dogs. These findings were not associated with clinical signs. They were consistent with pharmacological activities of betamethasone, as a corticosteroid, and demonstrated a systemic activity of this substance even at the recommended dosage.

Following overdoses, blister formation within the epithelium of the tympanic membrane, ulceration of the lining of the middle ear cavity and the haematological/biochemical changes are stated in the SPC (section 4.10).

The tolerance of OSURNIA was also confirmed in 5 field studies, including, overall, 697 dogs affected with otitis externa which were treated with OSURNIA, dogs treated with a negative control(n=209), or positive control groups, treated with Easotic (hydrocortisone aceponate/miconazole nitrate/gentamicin sulphate) (n=248) or Posatex (mometasone furoate/posaconazole/orbifloxacin) (n=41). The youngest dog was 2 months old, and the lightest dog weighed 1.4 kg (warnings are stated in the SPC in this regard in section 4.5)). In all field studies, the test product was well tolerated, with no serious adverse effects that were related to the product. No hearing disturbances were observed.

Licking of the product by another animal that lives in the same home as the treated dog is possible. However, firstly the oral toxicity of the product is very low and from a tolerability study that was conducted by using non-toxic dyes to follow physical progression of the gel onto the aural canal (see Part 4. Tolerance Study CRA 09-123, 4a1- pharmacol - cra09123), it appeared that that the product rapidly "left" the auricular pinnae. Thus, the risk of contact with the product by another dog when the treated dog returns home was considered to be very low. The risk of an accidental ingestion of the product by another animal was also considered as negligible.

In healthy dogs, the absorption of the product was considered as relatively low (order of ng/ml), although non-pivotal and pivotal tolerance studies showed that betamethasone was sufficiently absorbed to induce systemic effects (decreased cortisol levels). However, tolerance studies were conducted in dogs without auricular lesions. In field studies, dogs were affected with otitis. Thus, because of scratching, and, then, ulceration or inflammation, outer ear epithelium may be abraded and then the absorption may be higher than through intact epithelium. Although the observed effect in healthy dogs was not correlated to any clinical or pathological signs, the decrease in cortisol levels was added to the SPC (section 4.6). The safety of the product has not been assessed in dogs during pregnancy and lactation, and because of known teratogenic effects of betamethasone in rodents, the use of the product is contraindicated in pregnant bitches (sections 4.3 and 4.7).

Overall conclusion on tolerance

Tolerance in the target species (dogs) was well documented and the provided data were sufficient to confirm the safety of the product when used at the recommended dose and in the case of overdose.

Observed systemic effects were mainly related to pharmacological properties of the betamethasone component, and consisted mainly in decreased cortisol levels after ACTH stimulation. Dose-dependent decreased cortisol levels were observed in all treatment groups after product's instillation (before and after ACTH stimulation), although the findings were not correlated with any pathological or clinical signs, and were reversible. This observation is reflected in the SPC (sections 4.6 and 4.10).

Betamethasone was sufficiently absorbed to have systemic effects. As the safety of the product has not been assessed in dogs during pregnancy, and because of the known teratogenic effects of betamethasone in rodents, the use of the product is contraindicated in pregnant bitches.

Some slight local reactions (as epithelial blister in ear canal, and ulceration of the lining of the middle ear cavity) were reported in the case of over dosage, but they did not alter the hearing function. They are stated in the SPC.

Other haematological/biochemical changes were noted in 5X dosed dogs. This observation is stated in the SPC (section 4.10).

In field studies, the youngest treated dog was 2 months old, and the lightest weighed 1.4 kg. A warning is included in the SPC (section 4.5).

Field trials

The clinical documentation included several pilot studies and three large-scale field trials conducted in EU, USA and Japan. The pilot studies using a close-to-final formulation were considered to be of limited importance.

The pivotal field trials were GCP-compliant, randomised, blinded, multicentre and conducted in various geographic area with various breeds of dogs of different age and weight groups. Dogs were affected mainly, but not exclusively, by erythematous ceruminous and non-recurrent bilateral otitis. Infections were caused by *M. pachydermatis*, *S. pseudintermedius*, streptococci and other bacteria or fungi (alone or in mixed infection). The disease characteristics were well balanced between groups and representative of the proposed indication.

The pivotal EU trial (INT-11-011, 2013) was performed in multiple sites throughout France, Germany, and United Kingdom. Thirty veterinary clinics were involved including 286 dogs. Dogs of at least 8 weeks of age were included provided they presented otitis externa with evidence of bacterial and/or fungal infection on cytology and total clinical score of at least 5 out of 12. The majority of dogs had bilateral otitis externa (72%) at enrolment. In 204 cases (72%) the otitis was of erythematous ceruminous type and in 81 (28%) cases the otitis was suppurative. Among all dogs, 35 (12%) and negative culture results, 74 cases (26%) had only yeast cultured, 60 cases (21%) had only bacteria cultured and 115 cases had both yeasts and bacteria culture. The population was evenly distributed between treatment groups.

The study was designed to show non-inferiority of OSURNIA when compared to a positive control product (CP) containing hydrocortisone aceponate, miconazole nitrate and gentamicin sulphate. Among the 286 enrolled dogs, 148 dogs were treated twice with OSURNIA, seven days apart, and 138 dogs with the CP for five consecutive days. Prior to the first administration, the entire ear canal was cleaned with saline.

The primary efficacy endpoint was the mean reduction percentages over baseline in the total clinical score. This percentage of reduction which represents the improvement observed at 28 days after initial treatment was of 62.5% and 63.4% in the OSURNIA and CP group, respectively. Non-inferiority could be established since the upper bound of the two-sided 95% confidence interval for the difference in total clinical score was 7.9% (57.7 to 67.4% in the OSURNIA group and 58.3 to 68.4% in the CP group). As this difference was not higher than the accepted difference 0.15 (delta) x 63.4% = 9.5%, the non-inferiority was accepted.

No significant difference was found for secondary endpoints except for the speed of response which was slightly better for the CP group. The total clinical scores at the time of the second administration of OSURNIA decreased by 47% and 56% in the OSURNIA and CP group, respectively ($p < 0.001$).

The bacteriological response was 60% in both treatment groups. The bacteriological response on D28, for cases initially infected with *S. intermedius* was of 65% (44/68) and 52% (34/65) in the OSURNIA and CP group, respectively. The bacteriological response on D28, for cases initially infected with *streptococci* was 47% (9/19) and 64% (7/11) in the OSURNIA and CP group, respectively. Furthermore, the bacteriological response on D28 for cases initially infected with *E. coli* and *Pseudomonas* were lower33% (3/9) and 35% (6/17), respectively in the OSURNIA group and 50% (3/6) and 70% (14/20) in the CP group. The fungal response (mainly for *Malassezia pachydermatis*) was 76% and 69% in the OSURNIA and CP group, respectively. Due to low enrolment of cases with some pathogens, no firm conclusion could be drawn. The clinical success rate was 74% and 72%, respectively, in the OSURNIA and CP group 28 days after

treatment, and of 72% and 66%, respectively, 56 days after treatment. Cytology scores decreased similarly in both groups. The incidence of relapse rate was of 11% in both groups.

The USA trial (GSO-12-001, 2013) using the same dose and posology as in the EU trial demonstrated the superiority of OSURNIA to placebo treatment. Among 284 enrolled dogs, 190 dogs were treated with OSURNIA and 90 dogs with the placebo (same formulation without active substances). Prior to the administration of the products (placebo or OSURNIA) on D0 (only), the entire ear canal was cleaned with saline. On day 45, the treatment success rate was significantly higher in OSURNIA treated dogs (65.4%) than in the placebo treated dogs (43.6%; p=0.0073). The high success rate observed in the placebo group may be explained by the effect of cleaning the ear before the first administration and the protective film of the formulation on the surface of the ear canal. The bacterial and fungal cure rate could not be assessed because ear swabs were only taken in case of treatment failure. The clinical success rate on D45 after treatment for dogs infected at the time of enrolment with *M. pachydermatis* was of 73.4% and 51.5% for OSURNIA and placebo respectively. The success rate for dogs infected with *S. pseudintermedius* alone was of 70.6% and 70% for OSURNIA and placebo, respectively; while in mixed infection (*M. pachydermatis* and *S. pseudintermedius)* the success rate was 70.7% and 38.9% for the OSURNIA and placebo, respectively. The success rate for other pathogens (*P. aeruginosa,* β-hemolytic streptococcus species*, E. coli* or *P. mirabilis* alone or in combination with *M. pachydermatis* and/or *S. pseudintermedius*) were low (less than 50%). Moreover, the number of pathogens present at inclusion was low. This study showed the effectiveness of the product in the intended indication for mixed infections caused by *M. pachydermatis* and *S. pseudintermedius*.

The trial in Japan (JPN-10-001, 2012) compared the efficacy of OSURNIA to a positive control product (authorised in the EU) containing gentamycin sulfate, betamethasone valerate (1 mg as betamethasone) and clotrimazole. Among 72 enrolled dogs, 71 cases were assessable (49 dogs treated with OSURNIA and 22 with the CP). The pathogens mainly isolated at inclusion were *S. intermedius* and *M. pachydermatis.* There was no significant difference between groups for the percentage of improvement of the total clinical scores on D28 (approximately 78% in both groups) and for the efficacy rate (82.2% and 73.7% for OSURNIA and CP respectively). Some haematological changes were observed in the OSURNIA group but these findings were not associated with clinical signs and were therefore not considered relevant.

On the basis of the evidence provided by the three pivotal studies, OSURNIA was shown to be effective and safe for the treatment of acute otitis externa. The data confirmed that the same amount of product may be applied whatever the weight of the animal, the breed and the disease characteristics. The speed of response was lower on D7, and a second application was performed seven days after the first application. However, the clinical success or improvement in the total score was achieved 21 days after the second application. This has also been reflected in the SPC (section 4.9).

The applicant demonstrated the superiority of OSURNIA over a placebo but also the non-inferiority over a control product.

A warning was included in SPC section 4.4 to encourage an appropriate diagnosis before use of an antimicrobial treatment.

Overall conclusion on efficacy

OSURNIA contains three active substances, an antibiotic, an anti-fungal and a glucocorticosteroid. The applicant justified the combination by the need to cover a broad antibacterial and antifungal spectrum to treat otitis associated with bacteria and fungi.

Florfenicol is an analogue of chloramphenicol with bacteriostatic action against bacteria commonly associated with canine otitis externa, while terbinafine has fungicidal activity against *Malassezia pachydermatis.* Betamethasone acetate is a glucocorticosteroid and has anti-inflammatory action.

The CVMP considered that the risk of resistance development seemed unlikely and not highly critical for this ear gel product used in individual companion animals.

After administration of the product, as recommended, concentrations of florfenicol and terbinafine in the ear canal of healthy dogs were largely higher than the MIC of susceptible target pathogens. Systemic absorption of the three active substances was low; however, betamethasone absorption might potentially lead to some adverse effects systemically.

Dose rate of each component of the fixed combination, as well as the frequency of treatment (repeated administration) was sufficiently justified.

Tolerance in dogs was well documented and the provided data were sufficient to confirm the safety of the product when used at the recommended dose and in the case of overdose. Observed systemic effects were mainly related to the betamethasone component, and consisted mainly in decreased cortisol levels. However, as the product has not been assessed in dogs during pregnancy, and because of the known teratogenic effects of betamethasone, the use of the product is contraindicated in pregnant bitches.

The efficacy and clinical safety of OSURNIA were tested in three pivotal GCP-compliant large-scale field trials conducted in EU, USA and Japan. In the selected populations of dogs included in these studies the claims of OSURNIA were supported in case of otitis externa caused by florfenicol-sensitive bacteria and *Malassezia pachydermatis*. Satisfactory success rates were demonstrated against infections with *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*.

Somehow limited effect has also been shown in dogs affected by other pathogens (streptococci, *E. coli, Pseudomonas* spp.); however, the success rates and the number of cases were too low to demonstrate efficacy satisfactorily.

Part 5 – Benefit-risk assessment

Introduction

OSURNIA is an ear gel to be administrated as a single administration to dogs with otitis externa, treatment should be repeated 1 week later.

This product contains three active substances: florfenicol, terbinafine and betamethasone acetate. Terbinafine is a new active substance in veterinary medicine, although used in human medicines since the 1990's. The substance florfenicol is not new in veterinary medicine but has to date not been authorised for use in dogs. This is a new fixed combination of new and known substances. The application is made in accordance with Article 12(3) of Directive 2001/82/EC: full applications for a product containing a new active substance.

Benefit assessment

Direct therapeutic benefit

OSURNIA is an ear gel including three active substances in a new fixed combination: florfenicol as an antimicrobial, terbinafine as an antifungal and betamethasone acetate as an anti-inflammatory agent.

The new combination of the three components has been satisfactorily justified taking into account the proposed indications.

The efficacy of the product against acute otitis externa and acute exacerbation of recurrent otitis externa caused by *Staphylococcus pseudintermedius* and *Malassezia pachydermatis* is well documented and fully demonstrated.

The applicant has demonstrated the efficacy of the product in the treatment of ear infections in three large clinical field studies conducted in Europe, USA and Japan. Superiority of OSURNIA versus placebo was shown in a USA study, whilst non-inferiority versus an approved control product was demonstrated in a well conducted European field study. The dose for each of the three components and duration of treatment (twice, at an interval of 7 days) has been satisfactorily explained.

Additional benefits

An additional benefit of OSURNIA is the low number of doses (two) of a medicine that is to be administered to an infected and probably painful dog's ear, as compared to more commonly available daily applications.

Risk assessment

Main potential risks have been identified as follows:

Quality:

The formulation and manufacture of OSURNIA is well described, and the specifications set will ensure that product of an appropriate and consistent quality will be produced. Manufacturing process validation for the largest proposed production scale batches is still outstanding but will be finalised before any such sized batches are placed on the market.

For the target animal:

The product is well-tolerated in the target species (dogs) as demonstrated in three well-conducted tolerance studies (up to 5 times the recommended dosage) and confirmed by three large field studies. Observed systemic effects were mainly related to pharmacological properties of the betamethasone component, and consisted mainly in dose-dependent decreased cortisol levels after ACTH stimulation. However, they were not correlated with any pathological or clinical signs and were reversible.

Effects of betamethasone acetate are also well known glucocorticosteroid effects and include embryotoxicity and teratogenic properties. In the absence of safety data in the target species, the use of OSURNIA in pregnant animals has therefore been contraindicated.

No particular concern is raised for terbinafine, already used in human medicine. The provided information on its toxicity is complete and does not pose a particular risk for use in dogs.

For florfenicol, a NOEL of 1 mg/kg was retained from a 52-week oral toxicity study in dogs based on increase liver weights.

Some slight local reactions (as epithelial blister in ear canal and ulceration of the lining of the middle ear cavity) were reported in the case of overdose. Moreover, the absorption of the different active substances has not been assessed in non-healthy ears, and in the case of abraded outer ear epithelium, absorption of substance might be increased. However, none of the changes altered the hearing function or resulted in clinical signs, and it was concluded that the product when used in line with the SPC recommendations is overall well tolerated.

For the user:

The product does not pose an unacceptable risk to the user when used in accordance with the SPC. Appropriate warning sentences have been included in the product information to ensure the safety of the user, including potential accidental ingestion by a child.

For the environment:

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

Specific potential risks:

Antimicrobial resistance:

The use of florfenicol for the first time in dogs, a companion animal, raised some question about the antimicrobial resistance transfer from companion animals to people. Considering the data provided, the risk of development of resistance, although possible, seems not to be highly critical for this product.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

The product has been shown to be efficacious for the treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*.

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

It is well tolerated by the target animals and presents a low risk for users and the environment and appropriate warnings are included in the SPC and other product information.

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

Conclusion

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

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