10 October 2024
EMA/489190/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for DuOtic (EMEA/V/C/006102/0000)

INN: Betamethasone acetate / Terbinafine

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Introduction

The applicant Dechra Regulatory B.V. submitted on 3 October 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for DuOtic, through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 16 May 2023 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

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

For the treatment of otitis externa associated with *Malassezia pachydermatis*.

The active substances of DuOtic are betamethasone acetate and terbinafine.

Betamethasone acetate belongs to the diesters class of glucocorticosteroids with a potent intrinsic glucocorticoid activity which relieves both inflammation and pruritus. Terbinafine is an allylamine with a pronounced fungicidal activity. It selectively inhibits the early synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi.

The target species is dogs.

DuOtic ear gel contains 10 mg of terbinafine and 1 mg of betamethasone acetate and is presented in packs containing 2 tubes, 20 tubes and 40 tubes.

The rapporteur appointed is Paul McNeill and the co-rapporteur is Anna Wachnik-Święcicka.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 10 October 2024, the CVMP adopted an opinion and CVMP assessment report.

On 22 November 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for DuOtic.

Scientific advice

The applicant received scientific advice (EMA/CVMP/SAWP/238625/2018) from the CVMP on 21 June 2018. The scientific advice pertained to the safety and efficacy of the dossier.

The advice provided to the applicant largely related to the applicability of data assessed in the context of the MAA for Osurnia to the current application, and the design of the pivotal clinical efficacy trial. The applicant largely followed the advice provided by CVMP, and any deviation from advice was suitably justified by the applicant.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) with reference number *PSMFDechraGroup,* has the services of a qualified person responsible for pharmacovigilance, and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

DuOtic contains two active substances, betamethasone acetate and terbinafine.

Manufacture of the active substance betamethasone acetate takes place within the EEA. A QP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an audit by a third party.

Manufacture of the active substance terbinafine takes place within the EEA. A QP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an audit by a third party.

Finished product

Batch release of the finished product take(s) place at Genera d.d., Zagrebacka Zupanija, Croatia. A Manufacturing Authorisation was issued on 16th November 2020 by the Croatian Competent Authority. A GMP certificate issued by the Croatian Competent Authority is available in Eudra GMDP. The certificate was issued on 16th November 2020, referencing an inspection on 8th July 2022.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file was considered to be in line with legal requirements.

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

Part 2 - Quality

Composition

The product is an ear gel containing 10 mg/ml of terbinafine and 1.0 mg/ml of betamethasone acetate. The product is formulated as an auricular gel for a single intra-auricular application to each affected ear and this is repeated 7 days later. Other ingredients are butylhydroxytoluene, oleic acid, hydrogenated soybean lecithin, Hypromellose 2910, propylene carbonate and glycerol formal.

It is packed in a single use, aluminium laminate tube with a HDPE product contact layer and white HDPE shoulder and puncture point membrane seal. The cap consists of a polypropylene puncture point screw cap with a bonded soft TPE applicator tip. The product is packed in a cardboard box containing 2, 20 or 40 tubes (each tube containing 2.05 g of the veterinary medicinal product of which a single dose of 1.2 g can be extracted). An extraction study, a migration study as well as a sorption study have been performed on the packaging. There is a loss of about 3% of terbinafine due to migration of this active substance into the polyethylene layer of the primary packaging. The migration occurs over the course of 7-9 weeks before reaching saturation.

The pack sizes are consistent with the dosage regimen and duration of use.

Containers and closure system

The primary packaging is composed of a tube sealed with a connected soft, twist-and-use tip. The tube is composed of the body and the white HDPE shoulder and puncture point membrane seal. The body is an aluminium laminate with a HDPE product contact layer. The soft tip consists of polypropylene puncture point screw cap, with a soft applicator tip. Satisfactory specifications have been provided for the packaging materials along with declarations of compliance with Commission Regulation 10/2011 for plastic materials and articles intended to come into contact with food and the relevant monograph of the Ph. Eur. Information on the secondary packaging has been provided.

Product development

The proposed product was formulated to be very similar to the formulation of the product Osurnia ear gel for dogs (EMA/V/C/03753/0000) for which Dechra Regulatory B.V. is also the MAH. The main difference is that the proposed product does not contain the antibiotic florfenicol, in order to treat yeast related infections only, and to avoid the unnecessary use of an antibiotic and as a consequence there are minor differences in the excipients. The manufacturing process of the proposed product is the same as for Osurnia ear gel. The batch size of the registration/clinical batches is the same as the commercial batch size of Osurnia ear gel. The primary packaging is also the same for both products.

Because of the similarity in the formulations of both products, no new formulation development has been performed for the proposed product, rather, the 'Pharmaceutical development report' for Osurnia ear gel has been provided. Given that the difference between the formulation of Osurnia and this new product is only the absence of 10 mg/ml of one active substance with very minor consequential differences in four excipients in the formulation, the absence of development data specific to this formulation is considered acceptable.

The components of the formulation are well known and controlled in accordance with their respective European Pharmacopoeia (Ph. Eur.) monographs with the exception of the active substance terbinafine, which is not monographed in any pharmacopeia, and the excipients Phospholipon 90H (hydrogenated soybean lecithin) and propylene carbonate. Propylene carbonate is not monographed in the Ph. Eur. and is therefore controlled in line with its USP/NF monograph. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 2 of the SPC.

The active substance terbinafine and the excipient hydrogenated soybean lecithin are controlled in line with in-house specifications, which are the same as those approved for the product Osurnia ear gel for dogs. The formulation development report for Osurnia which is included in the dossier discusses the rationale for the choice and optimisation of the excipients used in the formulation and its critical quality attributes. Comparative data for DuOtic and Osurnia is provided in Part 4 demonstrating that the physicochemical parameters such as viscosity and pH, which are critical to the dosage form are the same for both products. Preservative efficacy studies were provided demonstrating that the product is self-preserving.

Description of the manufacturing method

The manufacturing process consists of a number of mixing steps with the excipients and active substances added sequentially with mixing and rinsing of the containers between additions. Following the final addition, the mixture is heated under vacuum and upon cooling a gel is formed and the bulk product is then filled into the final primary packaging. The finished product is extracted from the tube by pressing the tube between two fingers. Therefore, an overfilling of the tube is required to allow the extraction of the 1.2 g (1 ml) single dose. It was determined that filling the tube with 2.05 g of the gel, resulted in the desired deliverable amount of 1.2 g of gel. Nitrogen is used for sparging throughout the manufacturing process. The process is considered to be a standard manufacturing process and the in-process controls during the heating step are appropriate for the manufacture of a gel. In addition, equipment used in the manufacturing process has been specified by type and working capacity.

A commercial batch size range is proposed and the manufacturing formula includes calculation of the potency adjustments performed. A process validation report is provided for two batches within the proposed commercial batch size range. Process validation is provided for two of the largest proposed commercial scale batches. In addition, the process is almost identical to that of Osurnia. Process validation for two batches at time of submission is therefore considered acceptable. Data has also been provided to support a proposed bulk hold time.

Control of starting materials

Active substance

The finished product contains two active substances: betamethasone acetate which is described in the Ph. Eur. and terbinafine which is not described in the Ph. Eur. Data for both active substances is provided in ASMFs and separate reports for each ASMF are provide along with this report.

Betamethasone acetate

INN: Betamethasone Acetate

Chemical name:	9-Fluoro-11β, 17, 21-trhydroxy-16β-methylpregna-1,4-diene-3,20-dione 21 acetate
Other names:	Pregna-1,4-diene-3,20-dione,9-fluoro-11,17-dihydroxy-16-methyl-21-(acetyloxy)-,(11β, 16 β)-
CAS number:	987-24-6
Molecular formula:	$C_{24}H_{31}FO_6$
Molecular weight:	434.51

Sufficient information has been provided on the nomenclature, structure and general properties of the active substance. The manufacturing process for betamethasone acetate consists of two synthetic steps. A synthetic pathway is provided that includes the raw materials, solvents and reagents used, along with a brief description of the process. Satisfactory data has been provided on the characterisation of the active substance. Acceptable information has been provided for related substances, residual solvents and elemental impurities. The active substance specification includes tests for appearance, identity (IR, TLC), specific optical rotation, related substances (HPLC), water, assay (spectrophotometric), along with tests for residual solvents and microbial quality, and is considered to be acceptable. The test methods are well described and considered to be acceptable. The method validation provided is in accordance with the VICH guidelines VICH GL 1 and VICH GL2 and so is acceptable. Compliant comparative batch analysis data is provided for batches of the active substance. Satisfactory information regarding the reference standards has been presented. The active substance is packaged in double low-density polyethylene bags, closed with a plastic noose, placed in either a fibre carton drum or polypropylene containers with polyethylene caps, and then in carton boxes. Satisfactory specifications have been provided for the packaging. A declaration is provided of the compliance of the LDPE sealing disk with the current requirements of EU Regulation No 10/2011 on plastic materials and articles intended to come into contact with food. Stability data are provided for 16 batches of the active substance on long-term conditions of 25 °C/60% RH, and 5 batches on accelerated conditions of 40°C/75% RH. All results are within specification and the data provided supports the proposed retest period with no specific storage precautions required. An acceptable post-approval stability commitment was also provided.

Terbinafine

International Non-proprietary Name (INN): Terbinafine

IUPAC name: (2E)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hept-2-en-4-yn-1-amine

Chemical Names:

- (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalenemethanamine
- trans-N-methyl-N-(naphthylmethyl)-6,6-dimethyl-2-hepten-4-ynyl-1-amine
- 6,6-dimethyl-hept-2-en-4-ynyl)-methylnaphthalen-1-ylmethyl-amine

CAS number: 91161-71-6

Molecular formula: $C_{21}H_{25}N$

Molecular weight: 291.4

Sufficient information has been provided on the nomenclature, structure and general properties of the active substance. The manufacturing process for terbinafine consists of six steps. A synthetic pathway is provided that includes the raw materials, solvents and reagents used, along with a brief description

of the process and a flow chart. Satisfactory data has been provided on the characterisation of the active substance. Acceptable information has been provided for related substances, mutagenic impurities, residual solvents and elemental impurities. The active substance specification includes tests for appearance, identity (IR, HPLC retention time), water content, assay (titration), sulphated ash, related substances (HPLC) and residual solvents, and is considered to be acceptable. The test methods are well described and considered to be acceptable. The method validation provided is in accordance with the VICH guidelines VICH GL 1 and VICH GL2 and so is acceptable. Compliant comparative batch analysis data is provided for batches of the active substance. Satisfactory information regarding the reference standards has been presented. The active substance is packaged in transparent low density polyethylene bags in a second sealed polyethylene/aluminium-foiled bag, in fibre drums. Satisfactory specifications have been provided for the packaging. A declaration is provided of the compliance of the primary packaging with EU Regulation No 10/2011 on plastic materials and articles intended to come into contact with food, as amended, and with Ph. Eur. 3.1.3 and 3.1.4. Stability data are provided for 3 validation batches of the active substance at long-term conditions of 25 °C/60% RH, intermediate conditions of 30°C/75% RH and accelerated conditions of 40°C/75% RH. All results are within specification on long-term and intermediate conditions, but out-of-specification results were obtained on accelerated conditions. The data provided supports the proposed retest period, when stored at not more than 30°C. An acceptable post-approval stability commitment was also provided.

Excipients

Butylhydroxytoluene, oleic acid, Hypromellose 2910, glycerol formal and propylene carbonate are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. monographs, or the USP monograph for propylene carbonate. Nitrogen used for sparging during the manufacturing process complies with the Ph. Eur. monograph for 'Nitrogen' but including the tighter requirement for oxygen as per the Ph. Eur. monograph for 'Nitrogen, low-oxygen'. A copy of the USP monograph for propylene carbonate has been provided. Microbiological quality tests are included in the specifications for hypromellose and phospholipon, and a justification for the absence of control provided for the remaining excipients. The Ph. Eur. monograph for hypromellose includes functionality-related characteristics for viscosity with respect to its use as a viscosity-increasing agent, and the nominal viscosity of this excipient has been detailed.

The excipient hydrogenated soybean lecithin is tested according to an in-house monograph which includes tests for identification, content of phosphatidylcholine and lysophosphatidylcholine, triglycerides content, water, ethanol content, iodine value, heavy metals and microbiological testing. Test methods are provided and are in line with Ph. Eur. and/or USP test methods. A method verification report has been provided for the USNF method used for the content of phosphatidylcholine and lysophosphatidylcholine.

No novel excipients are used in the manufacture of the product.

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. A declaration is provided of the compliance of the product with the 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agent via human and veterinary medicinal products' EMA/410/01 Rev. 3.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product.

The finished product specification includes tests for appearance, viscosity, pH, water content, active substance identification, assay, antioxidant identification, antioxidant content, related substances, uniformity of dosage units and microbiological quality.

An elemental impurities risk assessment summary is provided. Evaluation was performed using Option 3, given that the maximum daily dose was calculated to be 2.4 g/day based on the recommended posology and worst-case scenario of the target species. Data is provided to demonstrate that levels of the elemental impurities to be considered for cutaneous exposure are present at less than 30% of the control threshold for cutaneous products and therefore routine control is not required. The data provided is in line with the requirements of ICH Q3D for cutaneous products.

The analytical methods used have been adequately described and appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for three commercial size batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The specifications proposed at the end of shelf-life are generally appropriate to control the quality of the finished product. The specifications proposed at the end of shelf-life are acceptable. Any differences between release and end of shelf-life specifications have been appropriately justified and supported by the stability data presented.

Stability data for three commercial size batches of finished product stored under long term conditions for 24 months at 25 ºC/60% RH, intermediate conditions for 12 months at 30 ºC/65% and for 6 months under accelerated conditions at 40 ºC/75% RH according to the VICH guidelines were provided. Photostability testing was performed on one batch in line with the requirements of VICH GL5 on photostability testing of new veterinary drug substances and medicinal products. A freeze-thaw study was conducted with one batch of the product subjected to up to three cycles of freezing (18 °C to -24 °C for minimum of 24 hours) and thawing (ambient temperature for a minimum of 24 hours).

No significant changes have been observed. For the antioxidant butylhydroxytoluene, decreasing trends were observed for all three batches on accelerated conditions which is in line with the sacrificial nature of antioxidants. Initial overall decreases are noted for all batches on all conditions for assay of terbinafine, which is in line with the absorption of terbinafine onto the primary packaging. In addition, some decreasing trends in terbinafine assay are noted.

Acceptable data has been provided to demonstrate that the product is also capable of complying with the proposed limit for terbinafine N-oxide and limit for the total related substances for terbinafine for the proposed shelf-life.

The proposed shelf-life of the veterinary medicinal product as packaged for sale is 2 years and is supported by the stability data provided, with the proposed storage precaution of "This veterinary medicinal product does not require any special storage conditions".

Overall conclusions on quality

The product was formulated to be very similar to the formulation of the product Osurnia ear gel for dogs (EMA/V/C/03753/0000). The product is a fixed combination veterinary medicinal ear gel containing 1.0 mg terbinafine (anti-fungal) and 10.0 mg betamethasone acetate (corticosteroid). Osurnia contains 10.0 mg florfenicol, 10.0 mg terbinafine, and 1.0 mg betamethasone acetate. As such, the difference is that the proposed product does not contain the antibiotic florfenicol, in order to treat yeast related infections only, and to avoid the unnecessary use of an antibiotic.

The applicant for the product is the MAH for Osurnia. Both Osurnia and the proposed product are produced at the same manufacturing site outside the EEA. The manufacturing process of the product is the same as for Osurnia ear gel. The batch size of registration/clinical batches is also the same as the commercial batch size for Osurnia ear gel. The primary packaging is also the same for both products. Because of the similarity of both products, the data in Part 2 is essentially the same as that approved for Osurnia. As such, information on the development, manufacture and control of the active substance and the finished product has generally been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Based on the review of the data on quality, the manufacture and control of the product are considered to be acceptable.

Part 3 – Safety documentation (Safety and residues tests)

DuOtic is a new fixed combination veterinary medicinal product (VMP) for dogs containing 10 mg of terbinafine and 1 mg of betamethasone acetate, indicated for the treatment of otitis externa associated with *Malassezia pachydermatis.* DuOtic is almost identical to the centrally authorised VMP Osurnia (for which the applicant is the marketing authorisation holder), with the exception of the absence of florfenicol from the candidate formulation. Minor adjustments have also been made to the amounts of four excipients to maintain total product weight and volume. Betamethasone acetate belongs to the diesters class of glucocorticosteroids with a potent intrinsic glucocorticoid activity which relieves both inflammation and pruritus. Terbinafine is an allylamine with a pronounced fungicidal activity. It selectively inhibits the early synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi.

CVMP scientific advice was requested in 2018, relating to safety and efficacy aspects concerning the development of DuOtic. The CVMP in its answers stated that no new toxicological studies for documenting the safety profile of betamethasone and terbinafine would be required. Safety data previously submitted with the MAA of Osurnia (for the active substances terbinafine and betamethasone acetate, and all excipients) was deemed acceptable and could be resubmitted with the MAA for DuOtic. However, a bibliographic search would be required to ensure that no new relevant pharmacological or toxicological data relating to betamethasone and terbinafine have been published since the granting of the original MA for Osurnia.

Safety tests

Pharmacology

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Note: No interaction was observed between the three active substances in Osurnia using both *in vivo* and *in vitro* models, with no overlapping pharmacodynamic action evident. Consequently, pharmacological interaction between betamethasone acetate and terbinafine as included in DuOtic is not anticipated.

Toxicology

The toxicological profile of betamethasone was assessed by the CVMP in the context of the establishment of maximum residue limits and in the authorisation of Osurnia. It is included in Table I of the Annex to Commission Regulation (EU) No. 37/2010. Betamethasone is also present in several marketed veterinary medicinal products in the EU.

The toxicological profile of terbinafine was also reviewed and assessed by the CVMP with the marketing authorisation application for Osurnia.

CVMP scientific advice was sought in 2018 for a new fixed combination of two active substances, an antifungal (terbinafine) and a corticosteroid (betamethasone acetate), for dogs presented as an ear gel in 2018 (EMA/CVMP/SAWP/238625/2018).

The CVMP response to the proposal not to conduct any new toxicology studies for DuOtic was as follows:

"*No new toxicological studies for documenting the safety profile of betamethasone and terbinafine are required. Safety data previously submitted with the MAA of Osurnia (for both active substances and excipients) can be used and should be resubmitted for the new product's MAA. However, a bibliographic research should be performed to ensure that no new relevant data that could modify the toxicological profile of betamethasone and terbinafine have been published since the application for Osurnia.*"

Following from this advice, the toxicological data on terbinafine and betamethasone as submitted with the application for Osurnia is summarised below. The applicant conducted bibliographic searches in September 2021 and October 2022 to determine if new relevant data on the toxicological profiles of terbinafine or betamethasone had been published since the authorisation of Osurnia.

Single-dose toxicity

Data from acute-dose studies indicate very low toxicity of active substances and the combination product. In rodents, acute oral dose LD_{50} for terbinafine, betamethasone and the combination product were >4000 mg/kg, >1000 mg/kg and >2000 mg/kg, respectively. No significant clinical abnormalities were noted in any of the studies reported.

Repeat-dose toxicity

Terbinafine

Extensive data from repeat-dose toxicity studies are available for terbinafine. Repeated oral administration for a minimum of 26 weeks in rats, dogs and monkeys resulted in a NOAEL of 30-60 mg/kg/day. Similarly, when applied topically for 4 weeks in rabbits, no systemic signs of toxicity were seen up to 60 mg/kg/day.

Betamethasone acetate

The EMA MRL summary report presented brief information on the repeat dose toxicity of betamethasone in rats, dogs and monkeys. No NOELs were established even at a low dose of 0.5 mg/kg given for several weeks in dogs. The NOAEL of 0.003 mg/kg/day betamethasone base, as determined in a 13-week dermal toxicity study in mice (identified in the bibliographic search), was used by the CVMP for the purpose of the quantitative risk characterisation for user safety assessment (adults and children).

Tolerance in the target species

See Part 4.

Reproductive toxicity, including developmental toxicity

Study of the effect on reproduction

Terbinafine

In a fertility and reproductive performance study in male and female rats, terbinafine was

administered orally at doses of 10, 50 or 250 mg/kg/day before mating and during pregnancy and lactation. Treatment with 10 or 50 mg/kg/day terbinafine showed no adverse effects. At a parental toxicity dose of 250 mg/kg, the pregnancy rate, mean number of implants, litter size and pup survival were decreased.

Betamethasone acetate
In a fertility study in rats, daily subcutaneous injection of betamethasone butyrate propionate at 0, 0.01, 0.1 or 1.0 mg/kg/day did not affect male and female fertility or the number of corpora lutea. Since reduced thymus weights were noted at 0.1 mg/kg/day, the overall NOEL was 0.01 mg/kg/day.

Reproductive studies with betamethasone dipropionate in rabbits, mice and rats using intramuscular doses up to 1, 33 and 2 mg/kg, respectively, indicated no impairment of fertility, but resulted in dose-related increases in foetal resorption in rabbits and mice. Studies in male rats at oral doses of up to 0.2 mg/kg/day and in female rats at oral doses of up to 1 mg/kg/day of betamethasone dipropionate indicated no impairment of fertility.

A number of studies in rats investigated the effect of antenatal administration of betamethasone on male development and reproductive performance. In three studies, pregnant rats were treated with 0.1 mg/kg intramuscular betamethasone on gestation days 12, 13, 18 and 19 and the effects in male offspring included impaired sperm quality, altered hormone levels, altered development of reproductive organs and reduced fertility. A multigeneration study that used the same intramuscular dosing regimen of pregnant rats found impaired development and structure of the epididymis in male offspring which was more pronounced in the F1 compared to the F2 generation.

Study of developmental toxicity

Terbinafine
Terbinafine was administered orally to male and female rats, at doses of 10, 50 or 250 mg/kg/day before mating and during pregnancy and lactation. Fertility and general reproductive performance of the offspring were normal in all dose groups.

In an embryo/foetotoxicity study conducted in rats, no teratogenic effects were demonstrated after oral gavage of terbinafine solution at 30, 100, or 300 mg/kg/day on days 6-15 of gestation.
In an embryo/foetotoxicity study conducted in rabbits, there was no effect on the reproductive parameters or foetal survival rates after orally gavaged terbinafine at 30, 100, or 300 mg/kg/day between days 6 to 18 of gestation.

No teratogenic effects were observed in rabbits administered 3% terbinafine gel dermally from days 6 through 18 of gestation at doses of 15, 45 or 150 mg/kg/day.

In a peri- and post-natal study in rats using doses of 30, 100 and 300 mg/kg/day, given during late pregnancy and lactation (day 15 of gestation to day 20 post-partum), terbinafine had no adverse effect on parturition and lactation or on the peri- and post-natal development and survival of the offspring.

Betamethasone acetate
Information from the EMA MRL summary report on betamethasone indicates a dose-dependent increase in incidence of embryotoxicity and teratogenicity in rats with a NOEL for teratogenicity of 0.4 mg/kg/day. In rabbits, at 0.01 mg/kg, foetal weights were significantly reduced and the incidences of foetuses with malformations and skeletal variations were significantly increased. The NOELs for both teratogenicity and foetotoxicity were 0.003 mg/kg/day. In these studies, betamethasone was administered subcutaneously, and a higher NOEL would be expected following oral administration.

Additional information on the developmental toxicity of betamethasone was identified by the applicant in a review of the published scientific literature. In rabbits, betamethasone dipropionate was shown to be teratogenic when given by the intramuscular route at doses of 0.05 mg/kg. When administered subcutaneously to pregnant rabbits during organogenesis at doses of 0, 0.000625, 0.0025 or 0.01 mg/kg/day, betamethasone dipropionate induced foetal toxicity, including foetal deaths, reduced foetal weight, external malformations and skeletal malformations at doses of 0.0025 mg/kg/day and above. The NOAEL identified in this study was 0.000625 mg/kg/day, which is lower than the NOEL for teratogenicity and fetotoxicity of 0.003 mg/kg/day reported in the betamethasone MRL summary report. The lower (and thus more conservative) NOAEL was used by the CVMP as a toxicological reference value in the quantitative user risk assessment.

Genotoxicity

Neither of the active substances demonstrated any mutagenic potential in both *in vitro* and *in vivo* studies. Following a review of published scientific literature, no additional risks were identified which would impact the toxicological profile of the candidate VMP compared to that for Osurnia. However, an *in vitro* assay conducted to evaluate the genotoxicity of terbinafine in human lymphocytes confirmed that terbinafine does not possess genotoxic properties: clastogenesis, DNA effects, aneugenesis, cytotoxicity and/or cytostasis were not observed in human lymphocytes under the conditions of the cited study.

Carcinogenicity

Two-year carcinogenicity studies in mice and rats with terbinafine suggested an increased incidence of tumours. However, a careful examination by a panel of expert reviewers concluded that there were no clear treatment related effects on the incidence of hepatocellular neoplasms. Following a review of published scientific literature, no additional risks were identified which would impact the toxicological profile of the candidate VMP compared to that for Osurnia. Carcinogenicity studies conducted with betamethasone dipropionate in mice (topical) and rats (oral), did not indicate a significant increase in the incidence of tumours in either male or female animals compared to the control groups.

Other requirements

Special studies

Terbinafine
Due to the observations of microscopic liver changes in the repeat dose toxicity studies in rats, additional studies were conducted to provide evidence for causality of changes.

The effect of terbinafine, terbinafine tert-butyl alcohol-metabolite, terbinafine carboxylic acid-metabolite and positive control article clofibric acid on peroxisomal enzyme activities was studied *in vivo* and *in vitro*. Results indicate that terbinafine-induced hepatic peroxisome proliferation in the rat is not solely due to the parent compound but rather to its metabolites and in particular to the carboxylic acid-metabolite. Similar observations were made *in vitro.*

However, neither terbinafine carboxylic acid-metabolite nor clofibric acid produced any significant induction of the above activities in human hepatocyte cultures, providing evidence for species differences in hepatic peroxisome proliferation. While terbinafine and the carboxylic acid-metabolite can at high doses produce peroxisome proliferation in rat hepatocytes, such compounds are most

unlikely to produce any significant peroxisome proliferation in human hepatocytes.

Eye and skin irritation

Terbinafine
Terbinafine in 2% cream was not a skin or ocular irritant in rabbits.

Combination Product (Osurnia – Florfenicol, Terbinafine and Betamethasone)
Osurnia was non-irritating and assigned to Toxicity Category IV in a 72-hour acute dermal irritation study in rabbits but was rated moderately irritating and assigned Toxicity Category III after 0.1 ml placed into the conjunctival sac in an acute eye irritation study in rabbits.

However, pharmacovigilance data from Europe and North America have identified cases of eye injuries as a result of accidental ocular exposure to the combination product Osurnia involving both dogs and humans. Clinical signs in people included corneal ulcers, eye irritation, conjunctivitis, redness, burning, stinging and itchiness in some veterinary personnel, pet owners and others who were near the dog during or after application of the product. Ocular exposure in humans mostly occurred when the dog shook its head during or just after application of Osurnia, although cases of indirect contact (product touched on animal's fur, then fingers touched the eyes) have also been reported. To mitigate the risk associated with ocular exposure, the product information for Osurnia was revised and appropriate warnings and precautions were added. The same warnings are proposed for inclusion for DuOtic.

Skin sensitisation

Terbinafine
Terbinafine did not induce dermal sensitisation in a guinea pig sensitisation study.

Combination Product (Osurnia – Florfenicol, Terbinafine and Betamethasone)
Osurnia was not a skin sensitiser in a local lymph node assay in female mice.

Observations in humans

Terbinafine
Terbinafine is approved for human use. Cases of overdosage have been reported, resulting in headache, nausea, epigastric pain and dizziness. In a post-marketing surveillance study, terbinafine was considered well-tolerated. The majority of the adverse events involved the skin and gastro-intestinal tract, and the effects were mild, transient and reversible. Serious adverse events due to terbinafine were reported in a Danish Register based on a 10-year study. The most prominent categories of adverse event were skin and subcutaneous tissue disorders followed by nervous system, hepato-biliary and GI disorders.

Betamethasone
Betamethasone has been used widely in human medicine for many years, as betamethasone alcohol and as various esters. Products are available for oral, IV or IM injection. Topical products are also available for the treatment of allergic or inflammatory conditions. Betamethasone preparations are generally well tolerated but the suppression of the immune system increases the susceptibility of patients to infections. It is contraindicated during pregnancy due to its embryotoxic and teratogenic effects. However, antenatal administration is used in cases of premature labour to hasten maturation of foetal organs and tissues and reduce perinatal mortality; epidemiological studies in which children were examined up to 12 years of age showed no adverse outcome.

Development of resistance and related risk in humans

DuOtic is for use in dogs only. Therefore, development of resistance by the human gut flora against the active substances is not relevant.

For data on resistance relating to clinical use of the veterinary medicinal product, please see Part 4.

Excipients

The candidate VMP formulation is qualitatively identical to that of the centrally authorised veterinary medicinal product Osurnia, apart from the exclusion of the antibiotic florfenicol. Quantitatively, both VMPs are essentially similar, noting that minor adjustments (approximately 0.9% increase) have been made to the concentrations of the following excipients - hydrogenated phosphatidylcholine, hypromellose 2910, propylene carbonate and glycerol formal - to maintain total product weight and volume. None of the proposed excipients are novel; they have been extensively used in foods and pharmaceuticals and the majority of them have been listed by the FDA as "Generally Recognised As Safe" (GRAS).

With regards to the excipients for which concentrations have been adjusted in the candidate formulation, it is noted that hydrogenated phosphatidylcholine and hypromellose are generally considered non-toxic and non-irritating. However, propylene carbonate has been classified as causing skin irritation and serious eye irritation and both components of glycerol formal were classified as causing serious eye irritation. Nonetheless, considering the very slight increases in the concentrations of these excipients, no adverse impact is anticipated regarding safety of the target species or users when the candidate VMP is used as recommended in the proposed product information.

User safety

A user safety assessment was provided, in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

It can be accepted that the candidate VMP, DuOtic, is of the same pharmaceutical form as Osurnia and is intended for administration in the same manner (aural administration) to the same target species (dogs) for a similar indication and at the same dose rate for the common active substances, i.e., terbinafine and betamethasone acetate. The formulations of each product are qualitatively identical, with the exception that florfenicol is not included in DuOtic.

Minor adjustments (approximately 0.9 % increase each) have been made to the concentrations of four excipients - hydrogenated phosphatidylcholine, hypromellose 2910, propylene carbonate and glycerol formal - to maintain total product weight and volume. It is not anticipated that these changes will adversely impact the risk to the user when the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC.

With regards to the quantitative risk assessment, MOEs for terbinafine (dermal or oral (hand-to-mouth)) revealed no unacceptable risk. However, when toxicological reference values derived from animal studies were used in calculating MOEs for betamethasone, the resulting values were below or around 1, thus indicating a potential risk to users and/or children. Given the established human use of betamethasone, the applicant considered it appropriate to further characterise the potential risks associated with dermal and oral exposure using human reference values. Based on the amended MOEs, it can be concluded that accidental dermal or oral exposure to DuOtic does not result in an

unacceptable risk for users, including children and pregnant women, provided the VMP is used as recommended in accordance with the proposed product information literature.

Similar user safety warnings as approved by the CVMP for the centrally authorised VMP, Osurnia, have been proposed for the candidate product and this is considered appropriate. These include warnings introduced for Osurnia as a result of post-authorisation pharmacovigilance reports relating to ocular irritation (in particular corneal ulcers) in users. The warnings proposed, including a recommendation for use by a veterinarian or under their close supervision, are considered to adequately communicate and mitigate risks.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided in accordance with VICH guideline GL6 and the CVMP guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1-Corr.1).

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing species. It can be concluded that the candidate formulation will not present an unacceptable risk for the environment when the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC.

Overall conclusions on the safety documentation: safety tests

The marketing authorisation application for DuOtic has been submitted in accordance with Article 42(4) of Regulation (EU) 2019/6 (optional scope). DuOtic is an ear gel containing 10 mg of terbinafine and 1 mg of betamethasone acetate, and is essentially similar to the centrally authorised VMP Osurnia, except for the removal of florfenicol and minor adjustments made to the amounts of four excipients (approximately 0.9% increase) to maintain total product weight and volume.

CVMP scientific advice was provided in 2018, relating to safety and efficacy aspects for the development of DuOtic. The CVMP advised that no new toxicological studies for documenting the safety profile of betamethasone and terbinafine would be required. Safety data previously submitted with the MAA of Osurnia (for both active substances and excipients) was deemed acceptable and could be resubmitted with the MAA for DuOtic. However, a bibliographic search would be required to ensure that no new relevant pharmacological of toxicological data relating to betamethasone and terbinafine have been published since the granting of the original MA for Osurnia.

Pharmacology:
No new data relating to pharmacodynamics of the product have been provided. In line with the previous CVMP scientific advice, the applicant has made reference to data submitted with the marketing authorisation application for the product Osurnia. No relevant data on the pharmacology of terbinafine or betamethasone has been identified by the applicant as being published since the authorisation of Osurnia.

The information included in sections 4.2 (Pharmacodynamics) and 4.3 (Pharmacokinetics) of the proposed SPC for DuOtic closely reflects that included under the corresponding sections for Osurnia apart from the omission of information relating to florfenicol, and the inclusion of susceptibility data obtained from clinical studies conducted for DuOtic. This is considered to be acceptable, and in line with CVMP scientific advice.

Toxicology:

The active substances in DuOtic are identical to those in the closely related product Osurnia, except for the removal of florfenicol. On this basis, the applicant considers that additional studies are not necessary to characterise the pharmacology of terbinafine and betamethasone. Reference is made instead to data submitted for Osurnia. Bibliographic searches were also conducted to ensure that no new relevant toxicological data relating to betamethasone and terbinafine were published since the authorisation of Osurnia.

The applicant has cited an old, non-GLP study in pregnant rabbits, from which a NOAEL of 0.000625 mg/kg/day was derived and which is lower than the NOEL for teratogenicity and fetotoxicity of 0.003 mg/kg/day reported in the betamethasone MRL summary report. The lower value identified was used by the CVMP in calculations for the quantitative risk assessment for pregnant women. This is a more conservative approach and is thus considered appropriate.

The absence of genotoxic properties of terbinafine in human lymphocytes was confirmed *in vitro*. Carcinogenicity studies in mice (topical) and rats (oral), demonstrated that betamethasone dipropionate did not significantly increase the incidence of tumours in male or female animals.

User safety:
A user safety assessment was provided, in accordance with the CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

The minor changes in quantitative composition of four of the excipients (compared to Osurnia) are not expected to adversely impact the risk to the user when the product is stored, handled, administered, and disposed of in accordance with the recommendations included in the proposed SPC.

Based on the amended MOEs (using human toxicological reference values), it can be concluded that accidental dermal or oral exposure to DuOtic does not result in an unacceptable risk for users, including children and pregnant women.

Similar user safety warnings as approved by the CVMP for the centrally authorised VMP, Osurnia, have been proposed for the candidate product and this is considered appropriate.

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

Part 4 – Efficacy

Pre-clinical studies

DuOtic 10 mg / 1 mg ear gel for dogs contains the active substances terbinafine (10 mg) and betamethasone acetate (1 mg). The proposed indication is the 'treatment of otitis externa associated with *Malassezia pachydermatis*' in the target animal species dogs.

DuOtic is very similar to 'Osurnia ear gel for dogs' (which contains florfenicol 10 mg, terbinafine 10 mg and betamethasone acetate 1 mg), except for the removal of florfenicol and minor adjustments made to the amounts of four excipients (approximately 0.9% increase) to maintain total product weight and volume.

In respect of data provided for Part 4 A, that is pre-clinical efficacy studies, the applicant has referred to those data already assessed by the CVMP in the context of the EU marketing authorisation application (MAA) for Osurnia. With the exception of information concerning the susceptibility / development of resistance of *Malassezia pachydermatis* to terbinafine, no new data concerning pharmacology, dose justification and confirmation and tolerance in the target animal species have been provided. It is noted that this approach was considered acceptable in scientific advice provided by CVMP in 2018 (EMA/CVMP/SAWP/238625/2018).

Pharmacology

Pharmacodynamics

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*.

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

Possible interactions (of betamethasone acetate on the MIC of terbinafine against *M. pachydermatis* and of terbinafine on the anti-inflammatory effect of betamethasone acetate) were suitably investigated in the context of the original MAA for Osurnia. It is therefore accepted that inclusion of these active substances in the fixed combination formulation of the candidate VMP will not negatively impact upon the efficacy of either substance.

The pharmacodynamics of the active substances terbinafine and betamethasone acetate have been suitably reported, and appropriate information has been proposed for inclusion in section 4.2 of the SPC.

Pharmacokinetics

Five non-GLP pilot and two GLP pivotal ear and plasmatic pharmacokinetic studies in dogs after auricular application were conducted and assessed by the CVMP in the context of the original MAA for Osurnia.

After administration of the product as recommended, concentrations of terbinafine in the ear canal of healthy dogs were substantially higher than the MIC of *M. pachydermatis.* Seven days after the first administration, mean concentrations of betamethasone acetate and terbinafine were 615

ng/mg and 5,870.5 ng/mg, respectively, while 7 days after the second administration, mean concentrations were 910 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 from ears were around 4–5 days.

Systemic absorption of the active substances was of the magnitude of ng/ml, and likely to occur over 2–4 days after administration. This aspect of pharmacokinetics (i.e., systemic absorption) is important to consider for the absorption of betamethasone.

It is concluded that the pharmacokinetics of the active substances terbinafine and betamethasone acetate have been suitably reported, and that relevant information has been proposed for inclusion in section 4.3 of the SPC.

Justification of the fixed combination

Justification for the fixed combination of terbinafine and betamethasone acetate in the candidate VMP has been provided with the following points highlighted:

- Otitis externa associated with yeast species (and no bacterial species) has been reported to occur in up to 26% of otitis externa cases.
- Use of an ear preparation containing an antibiotic in cases such as these does not constitute prudent or responsible use of antimicrobials, as the antibiotic component is not indicated at the time of use.
- The combination of an anti-inflammatory agent (betamethasone acetate) along with an antifungal agent (terbinafine) allows for treatment of inflammation in the ear, along with the fungal pathogen. Treatment of this inflammation lessens the contribution of inflammation to the pathogenic processes in otitis externa (inclusive of pain, reduced air flow, etc.).
- It has been suitably demonstrated that neither terbinafine nor betamethasone acetate interact with each other in a manner that negatively impacts upon the efficacy of either active substance.

Taking into account the requirements of the Guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005-Rev.1) and noting the similarity of the candidate product to the authorised VMP Osurnia, for which justification for the fixed combination (including florfenicol) has already been accepted by CVMP, the following points are also considered relevant to the justification:

- The active substances terbinafine and betamethasone acetate are both indicated in an inflammatory condition of the ear caused by a fungal agent, and extrapolation of the proposed posology from the authorised VMP Osurnia for the two active substances in the candidate VMP is appropriate and is further supported by the results of the pivotal clinical field efficacy trial. It is also noted that the pivotal clinical field trial was performed using the candidate VMP (i.e., the final conclusions on efficacy do not rely on extrapolation of data from another VMP).
- Unintended interactions that could lead to a negative impact on efficacy of either active substance and/or target animal tolerance have been suitably investigated and it is accepted that no significant interactions are reported.
- In respect of tolerance in the target animal species, while no new proprietary target animal tolerance studies have been submitted with the current application, it is noted that the only substantive difference in formulation between Osurnia and the candidate VMP is the absence

of florfenicol in the latter, and this is not expected to impact negatively on target animal safety. It is accepted that the possibility of interactions between the active substances that may impact on target animal safety has been suitably investigated and can be considered negligible.

- In respect of potential advantages, while the candidate VMP does not broaden the activity spectrum as compared to the VMP Osurnia, it is accepted that it does offer the opportunity for targeted therapy in cases of otitis externa associated with *Malassezia pachydermatis* that do not involve bacterial pathogens. It is also considered justified for therapeutic reasons to administer an antifungal agent concomitantly with an anti-inflammatory agent in cases of otitis externa, and also for reasons such as animal handling, and owner compliance (i.e., a reduction in number of treatments as compared to use of monoactive VMPs).

In conclusion, the fixed combination of the active substances terbinafine and betamethasone acetate in the candidate VMP is considered to have been suitably justified.

Development of resistance and related risks in animals

The risk of development of resistance of *Malassezia pachydermatis* to terbinafine has been addressed by reference to published literature, and proprietary data.

The mechanism of resistance to allylamines (including terbinafine) is usually associated with point mutations in the squalene epoxidase gene (ERG1) which results in impairment of allylamine binding. Biofilm production may also play a role. Resistance to allylamines is reported to be rare.

The applicant has presented two datasets comprising terbinafine MIC results in *M. pachydermatis* isolates cultured from dogs from the EU and the US with yeast-predominant otitis externa.

Samples from client-owned dogs that presented to veterinary clinics in Spain, France and Sweden (30 EU isolates), and across a number of US sites (30 US isolates) were assayed for terbinafine susceptibility. Similar results were found in both geographical regions, with MIC_{50} and MIC_{90} values of 0.12 and 0.25 µg/ml reported for both EU- and US-derived isolates.

Terbinafine MIC data for samples obtained from dogs enrolled in the pivotal clinical field efficacy trial were also reported. MIC_{50} values of 0.12 µg/ml were reported for the EU and US isolates. MIC_{90} values increased slightly between study Day 0 and study exit in both regions - from 0.25 µg/ml to 0.5 µg/ml in the US isolates, and from 0.25 µg/ml to 1 µg/ml in the EU isolates.

It is accepted that susceptibility of *M. pachydermatis* to terbinafine in samples obtained from clinical cases of otitis externa does not differ between the US and the EU. Although there are no published clinical breakpoints for terbinafine resistance in *M. pachydermatis*, the MIC results reported do not differ substantially (and are slightly lower) from the MIC for terbinafine reported in the SPC of Osurnia (MIC_{90} of 2 µg/ml).

Based on data presented and assessed in the context of the original MAA for Osurnia, concentrations of terbinafine achieved in ear cerumen at timepoints up to 35 days following the first of 2 administrations of the VMP are substantially greater than the MIC values in isolates from clinical cases. This information, when taken in the context of the results of the clinical efficacy trial, lends further support for the reported efficacy of the candidate VMP in the treatment of otitis externa associated with *M. pachydermatis*.

The current situation with regard to the risk of resistance development is considered favourable, and information concerning prudent use of the candidate VMP with a view to mitigating against the risk of resistance development has been included in the proposed SPC.

Dose determination and confirmation

Dose justification

No new proprietary data have been presented in support of dose determination and confirmation for the candidate VMP. Based on the similarity of the candidate formulation to that of the authorised VMP Osurnia (with the exception of the omission of florfenicol from the candidate VMP) and the lack of evidence for interaction between the active substances that could impact upon efficacy, the applicant has referred to the data submitted and assessed in the context of the original MAA for Osurnia (three field studies conducted in Europe and USA). The same posology is proposed in section 3.9 of the SPC for the candidate product as is approved for Osurnia: one tube (1 ml containing 10 mg terbinafine and 1 mg betamethasone acetate) per affected ear, with a repeated administration after 7 days.

When also taking into account the results of the pivotal clinical efficacy field trial submitted with this application, the approach of the applicant in respect of dose determination and confirmation is considered to be acceptable and to be in line with the scientific advice provided by the CVMP. The dose proposed and the frequency of administration for the candidate VMP is considered to have been suitably justified.

Tolerance in the target animal species

In support of tolerance in the target animal species, the applicant has referred to safety data that were assessed and considered acceptable in the context of the MAA for Osurnia. Two non-pivotal (one GLP-compliant and one non-GLP) and one pivotal (GLP-compliant) tolerance studies were conducted for Osurnia. These observations are further supplemented with target animal safety data gathered in the context of the pivotal clinical field trial submitted with this dossier.

The applicant has also provided a comparison of the physicochemical characteristics of Osurnia and the candidate product, and it is accepted that both formulations have very similar physicochemical characteristics inclusive of pH, water content, active substance concentrations and viscosity. Furthermore, both products are manufactured in the same facility, using the same raw materials (of the same grade and sourced from the same suppliers).

Taking into account that the proposed posology for the candidate product is the same as that for Osurnia, the approach of the applicant in respect of extrapolation of safety data from Osurnia to the candidate product is considered acceptable.

Target animal safety studies conducted with Osurnia showed that the 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 instillation (before and after ACTH stimulation), although the findings were not correlated with any pathological or clinical signs and were reversible.

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 (epithelial blisters in the 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 hearing function.

Haematological/biochemical changes were noted in dogs administered a 5-times overdose.

In field studies conducted for Osurnia, the youngest treated dog was 2 months old, and the lightest treated dog weighed 1.4 kg.

The safety data assessed in the pivotal clinical field trial submitted with this application are also taken into account. 239 animals were enrolled (and 120 were administered the candidate VMP) in this study. Following assessment of the safety data generated in this study, the following adverse events are possibly associated with treatment with the IVP: clinically significant increase in ALT (n=4) and in ALP (n=1) although it is noted that the latter was also seen in one control animal, and conjunctivitis (n=2) although no ocular exposure to the IVP was reported in these animals.

Based on the totality of data presented and noting the lack of proprietary target animal safety studies performed using the candidate VMP, it is expected that the SPC for the candidate VMP will reflect all relevant safety information as accepted for Osurnia, along with additional data from the pivotal clinical field trial, as appropriate.

Concerning sections 3.3, 3.4, 3.7 and 3.10 of the proposed SPC, it is noted that these are consistent with the corresponding sections of the SPC of Osurnia, and that no relevant safety information has been omitted.

Concerning section 3.6 of the SPC, the applicant has included all adverse events as they appear in the approved SPC of Osurnia and has added 'Elevated liver enzymes' as an uncommon adverse event, with the footnote: 'mainly transient elevation of alanine aminotransferase'.

It is accepted that when used in accordance with the proposed SPC, the candidate formulation will have an acceptable safety profile for the target animal species, dogs.

In summary, it is concluded that tolerance of the target animal species to the candidate VMP has been suitably investigated by the applicant.

Clinical trial(s)

The applicant has presented a well-designed GCP-compliant clinical field trial designed to evaluate safety and efficacy of the candidate VMP and which is generally in compliance with relevant guidance.

The study was designed as a superiority study and compared efficacy of the candidate formulation (DuOtic) to a saline control. The study was performed in two geographical territories (5 study sites / veterinary clinics in the EU (in Spain) and 13 in the US). Of the 239 dogs enrolled in the study, 65 were from the EU and 174 from the US. The applicability of study data obtained in the US to the EU is considered to have been established based on the similarity of terbinafine susceptibility data in *M. pachydermatis* isolates obtained from dogs with yeast-predominant otitis externa from multiple countries in the EU and the US (noting that these MIC data were all generated in the same laboratory). Furthermore, it is acknowledged that the concentrations of terbinafine achieved in the ear cerumen of treated dogs far exceeds the MIC levels reported for terbinafine, and that at present the situation regarding resistance development in *M. pachydermatis* to terbinafine is considered favourable.

The number of animals required for the study was suitably justified. The actual numbers enrolled were 239 dogs, with 197 dogs analysed in the per protocol population (PP) analysis of efficacy and 205 in the intention to treat (ITT) analysis. The dogs enrolled were approximately evenly distributed in respect of sex, and incorporated a diverse range of ages, body weights and breeds. In addition, the clinical cases of otitis encompassed acute (25.9%), sub-chronic (43.1%) and chronic (31%) otitis externa as well as including recurring cases. The study population is therefore accepted as

being suitably representative of the target population of animals that are intended to be treated with the candidate VMP.

The study was conducted with the final formulation of the candidate product with 1 ml saline administered as a control product at the same timepoints as the investigational VMP, i.e., 1 ml instilled in the horizontal ear canal on 2 occasions 7 days apart. Suitable provision for early exit from the trial due to lack of efficacy, or to treat developing / worsening otitis was provided to veterinarians and owners of enrolled dogs.

The inclusion and exclusion criteria described by the applicant are acceptable and the cytological criteria used to define eligible cases were suitable to rule out mixed / bacterial causes of otitis externa in so far as is possible. Those cases in which *M. pachydermatis* was not cultured were excluded from efficacy calculations but were included in assessment of all safety parameters.

The study design in respect of blinding, randomisation, number of visits (5 between study Day 0 and Day 45) and parameters evaluated in order to accurately assess efficacy and safety of the candidate VMP was appropriate.

The Otitis Index Scoring composite tool (OTIS3) was used as a clinical scoring system as published by Nuttall *et al.* and 'treatment success' defined as an OTIS3 score of ≤3 (provided no one parameter has a higher score at study exit than was recorded at day 0) was selected as the primary efficacy outcome parameter.

Concerning efficacy, analysis of the primary efficacy outcome variable 'treatment success' in both the per protocol (PP) and intention to treat (ITT) populations comprising 197 and 205 animals, respectively, was presented. The difference in the proportion of study animals considered to be a 'treatment success' at study exit between the treated and control groups was found to be statistically significantly different (62.86% compared to 20.00%, respectively ($p<0.0001$) in the ITT population and 62.75% compared to 18.95%, respectively ($p=0.0001$) in the PP population). That this difference is also considered to be clinically relevant is supported by the secondary outcome variable in which veterinarians and owners assessed clinical outcome based on clinical signs. Veterinarians considered 61.77% of treated animals to have a good or excellent response (compared to 12.63% of control animals) and animal owners considered 61.28% of treated animals to have a good or excellent response (compared to 24.21% of control animals) at study exit. It was noted that more dogs exited the study early due to perceived lack of efficacy in the control group (n=47) compared to the treated group (n=19).

Cytology data (a statistically significant difference in Least Square Means (LSM) for yeast counts (2.75 and 15.3 ($p<0.0001$) in the treated and control groups, respectively, at study exit) are suggestive of effective treatment of the causative pathogen *Malassezia pachydermatis* by terbinafine.

Safety of the candidate VMP was assessed in all enrolled animals (n=239) regardless of whether they were excluded from the efficacy analysis or exited the study early. The parameters assessed are considered to suitably reflect the expected adverse event profile (based on that of Osurnia) and take into account the fact that betamethasone is systemically absorbed to a degree following topical administration.

Based on the findings from this study, it is concluded that the following adverse events are possibly associated with treatment with the candidate product: clinically significant increases in ALT (n=4) and in ALP (n=1) although it is noted that the latter was also seen in one control animal, and conjunctivitis (n=2) although no ocular exposure to the product was reported in these animals. It is accepted that based on the safety data reported in this pivotal clinical field efficacy trial, the

candidate VMP has an acceptable safety profile for the target animal species, dogs, when used in accordance with the proposed SPC.

The conclusion that a single pivotal clinical field trial offers sufficient support for efficacy of the candidate VMP for the indication 'treatment of otitis externa associated with *Malassezia pachydermatis*' in dogs is accepted based on the following rationale. The similarity of the candidate VMP to the authorised VMP Osurnia (with the exception of the inclusion of the active substance florfenicol in the latter) is considered sufficient to permit extrapolation of dose determination and confirmation data for terbinafine and betamethasone acetate from Osurnia to the candidate product. There is no evidence that removal of florfenicol from the formulation will impact negatively upon the efficacy of terbinafine and betamethasone acetate. Efficacy has been suitably demonstrated (superiority over a placebo) in a single, large, multi-centre pivotal clinical field trial comprising a diverse study population representative of the animals for which the product is intended for use. It is therefore accepted that the candidate VMP is anticipated to be effective for the proposed indication under the expected conditions of use.

Overall conclusions on efficacy

Pharmacology

Pharmacodynamics

DuOtic contains two active substances, one anti-fungal and one anti-inflammatory component. The pharmacodynamics of the active substances terbinafine and betamethasone acetate have been suitably reported, and appropriate information has been proposed for inclusion in section 4.2 'Pharmacodynamics' of the SPC.

Pharmacokinetics

The pharmacokinetics of the active substances terbinafine and betamethasone acetate have been suitably reported, and relevant information has been proposed for inclusion in section 4.3 'Pharmacokinetics' of the SPC.

Justification of the fixed combination

A satisfactory justification for the combination product, in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005-Rev.1) was provided. The principal advantage claimed for the combination is that the combination of an anti-inflammatory agent (betamethasone acetate) along with an antifungal (terbinafine) allows for treatment of inflammation in the ear, along with the fungal pathogen. Treatment of this inflammation lessens the contribution of inflammation to the pathogenic processes in otitis externa (inclusive of pain, reduced air flow, etc.).

Development of resistance and related risks to animals

The current situation with regard to the risk of resistance development is considered favourable, and information concerning prudent use of the candidate VMP with a view to mitigating against the risk of resistance development has been included in the proposed SPC.

Dose determination and confirmation

The dose and frequency of treatment proposed for the candidate VMP (based on that approved for the authorised VMP Osurnia) is considered to have been suitably justified.

Tolerance in the target animal species

It is concluded that tolerance of the target animal species to the candidate VMP has been suitably investigated by the applicant. It is accepted that, when used in accordance with the SPC, the candidate VMP will have an acceptable safety profile for the target animal species, dogs.

Clinical trials

Efficacy has been suitably demonstrated (superiority over a placebo) in a single, large, multi-centre pivotal clinical field trial comprising a diverse study population representative of the target population in which the product is intended for use. Based on the results of this pivotal randomised, controlled clinical trial, it is accepted that the candidate VMP is anticipated to be effective for the proposed indication under the expected conditions of use.

Part 5 – Benefit-risk assessment

Introduction

DuOtic is an otic gel containing a fixed combination of 2 active substances: betamethasone acetate and terbinafine. The active substances are well-known.

The active substance betamethasone acetate belongs to the diesters class of glucocorticosteroids with a potent intrinsic glucocorticoid activity which relieves both inflammation and pruritus.

The active substance terbinafine is an allylamine with a pronounced fungicidal activity. It selectively inhibits the early synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi.

The product is intended for use in dogs for the treatment of otitis externa associated with *Malassezia pachydermatis*. The proposed dose is 10 mg of terbinafine and 1 mg of betamethasone acetate per affected ear with administration of the VMP repeated once after 7 days.

The application has been submitted in accordance with Article 8 of Regulation (EU) 2019/6 – full application.

Benefit assessment

Direct benefit

The benefit of DuOtic is its efficacy in the treatment of otitis externa associated with *Malassezia pachydermatis*, which was established in a well-designed clinical field trial conducted to an acceptable standard.

Additional benefits

DuOtic offers the opportunity for targeted therapy in cases of otitis externa associated with *Malassezia pachydermatis* that do not involve bacterial pathogens.

The fixed combination facilitates dog handling by reducing the total number of treatments to be given.

An additional benefit of the product 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 daily applications.

Risk assessment

Quality

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

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of DuOtic in accordance with the proposed SPC recommendations is generally well-tolerated.

The main reported adverse reactions include elevated liver enzymes (transient), deafness and impaired hearing (usually temporary), application site reactions and hypersensitivity reactions.

In the absence of data, use in pregnant and lactating bitches as well as in breeding animals is contraindicated.

Risk for the user

The candidate formulation is qualitatively identical to that of the centrally authorised veterinary medicinal product Osurnia, with the exception that the antibiotic florfenicol is not present in DuOtic. Quantitatively, both VMPs are essentially similar, although it is noted that minor adjustments have been made with respect to the concentrations of four excipients (hydrogenated phosphatidylcholine, hypromellose 2910, propylene carbonate and glycerol formal) to maintain total product weight and volume. The slight increases in concentration for these excipients are not considered to negatively impact the safety profile of DuOtic, which is considered acceptable.

Risk for the environment

DuOtic 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.

Risk management or mitigation measures

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

User safety

Similar user safety warnings as approved for the similar centrally authorised VMP, Osurnia, have been proposed for the candidate product and this is considered appropriate. These include warnings introduced for Osurnia as a result of post-marketing pharmacovigilance reports relating to ocular irritation (in particular corneal ulcers) in users. The warnings proposed, including a recommendation for use by a veterinarian or under their close supervision are considered to adequately communicate and mitigate risks.

Environmental safety

Adverse environmental effects are not expected when the veterinary medicinal product is used as described in the proposed SPC. Special precautions for the use of the VMP to reduce risks for the environment are not considered necessary.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: "For the treatment of otitis externa associated with *Malassezia pachydermatis*."

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

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Veterinary Medicinal Products (CVMP) considers that the application for DuOtic is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) No 2019/6).

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.