6 October 2022
EMA/834904/2022
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Mometamax Ultra (EMEA/V/C/004987/0000)

INN: gentamicin / posaconazole / mometasone furoate

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

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Introduction

The applicant Intervet International B.V. submitted on 21 April 2021 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Mometamax Ultra, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 March 2018 as Mometamax Ultra contains an active substance (posaconazole) which was not authorised as a veterinary medicinal product in the Union on the date of entry into force of Regulation (EC) No 726/2004.

At the time of submission, the applicant applied for the following indication: treatment of otitis externa associated with strains of bacteria susceptible to gentamicin (*Staphylococcus pseudintermedius*, *Streptococcus canis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*) and fungi susceptible to posaconazole (*Malassezia pachydermatis*).

The active substances of Mometamax Ultra are gentamicin sulfate, posaconazole and mometasone furoate monhydrate. Gentamicin is an aminoglycoside bactericidal antibiotic which acts by inhibiting protein synthesis, posaconazole is a broad-spectrum triazole antifungal agent, whilst mometasone furoate is a corticosteroid with high topical potency. The target species is dogs.

Mometamax Ultra ear drops suspension contains 8600 IU of gentamicin (as sulfate), 2.6 mg of posaconazole and 2.1 mg of mometasone furoate (as monohydrate) per ml and is presented in packs containing 1 bottle containing 20 doses of 0.8 ml each. The recommended dose of 0.8 mL contains 6880 IU gentamicin (as sulfate), 2.08 mg of posaconazole and 1.68 mg of mometasone furoate (as monohydrate).

The rapporteur appointed is Keith Baptiste and the co-rapporteur is Sylvie Louet.

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

On 6 October 2022, the CVMP adopted an opinion and CVMP assessment report.

On 22 November 2022, the European Commission adopted a Commission Decision granting the marketing authorisation for Mometamax Ultra.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (Version 3.0 dated 1 July 2018) which fulfils the requirements of Directive 2001/82/EC. Based on the information

provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

The applicant has submitted a "Declaration form for submission of DDPS" (Detailed Description of the Pharmacovigilance System) already approved by member states during a previous MR/DC/centralised procedure.

Manufacturing authorisations and inspection status

Batch certification takes place within the EEA at Vet Pharma Friesoythe GmbH (Friesoythe, Germany). The site has a manufacturing authorisation issued on 10 May, 2021 by Staatliches Gewerbeaufsichtsamt Oldenburg. GMP certification, which confirms the date of the last inspection and shows that the site is authorised for batch certification.

A GMP declaration for all active substance manufacturing sites including the separate micronisation site of gentamicin was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on on-site audits by MSD GMP Auditing Group. The dates of the on-site audits did not exceed 3 years.

Overall conclusions on administrative particulars

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

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

Part 2 - Quality

Composition

The finished product is an ear drops suspension of three micronised active substances, gentamicin (as sulfate), mometasone furoate (as monohydrate) and posaconazole, in viscous paraffin base.

Other ingredients are: paraffin liquid (vehicle) and plasticized hydrocarbon gel which consists of polyethylene and mineral oil and acts as a thickening agent.

The quantity of gentamicin (as sulfate) is expressed in IU in the composition in module 3.2.P.1 and in section 2 of the SPC as it is being assayed by microbiological test. Quantities of mometasone furoate (as monohydrate) and posaconazole are expressed in mg.

Containers

The container closure system selected is a white high-density polyethylene (HDPE) bottle closed with a white low-density polyethylene (LDPE) cap. The enclosed LDPE press-in bottle adapter (PIBA) is pressed into the bottle before use. Each bottle contains 20 doses. For each administration, a new syringe is used to deliver a 0.8 ml dose. Twenty polypropylene graduated syringes of 1.0 ml capacity will be packaged in the carton box together with the bottle and press-in-bottle adapter (PIBA).

The material complies with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements.

The suitability of the container closure system has been evaluated as part of the pharmaceutical development section (3.2.P.2. Pharmaceutical development) and during stability testing of the finished product.

In general, acceptable specifications are established for the primary packaging components and they include identification tests by IR. Migration studies have been performed on the bottle, PIBA and cap investigating potential leachables. All identified leachables were below the toxicological evaluation/safety concern threshold, calculated based on the less-than-lifetime approach for dogs in line with the guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products (EMA/CVMP/SWP/377245/2016).

Development pharmaceutics

The product development has been described, the choice of excipients is justified and their functions explained.

The ear drops suspension contains three micronised active substances gentamicin (as sulfate), mometasone furoate (as monohydrate) and posaconazole, which are suspended in a viscous paraffin base.

The following physicochemical attributes have been investigated as they are critical for the performance of the finished product: solubility of actives in paraffin liquid, rheological characterisation, viscosity, settling studies, resuspendability, particle size, crystallinity and morphology.

The physical properties of the active substances are well characterised, including particle size distribution and polymorphic form, and routinely controlled.

Paraffin liquid is the major component of the vehicle. The viscosity of the vehicle is increased with a thickening agent plasticized hydrocarbon gel, which consists of polyethylene in mineral oil. Plasticized hydrocarbon gel is a significant component of the finished product.

It has been documented that the syringes packaged in the carton box together with the bottle and PIBA are suitable for the intended use. Dose delivery/dose accuracy studies in accordance with Ph. Eur. 2.9.27 (Uniformity of mass of delivered doses from multidose containers) show that 15 seconds shaking ensures homogeneous suspension ensuring that the amount of active substances is uniform and that twenty doses of 0.8 ml can be delivered from one bottle with the proposed syringe.

The formulation used during clinical studies is the same as that intended for marketing.

The justification of the proposed container closure system is presented. The current stability data indicates that the container closure system is suitable.

In line with the Guideline on plastic immediate packaging materials (EMEA/CVMP/205/04), interaction studies have been conducted investigating the possibility of migration of components of the external layers into the medicinal product and sorption. The conclusion on migration is that none of the possible leachables will exceed the safety concern threshold during the shelf-life period of the finished product. The sorption of the active substances to the primary packaging has been studied indirectly following assay of the active substances during the stability studies. The stability study results indicate lack of sorption.

Minimum fill test was performed as per USP <755> Minimum Fill to ensure that the amount of drug product filled into the bottle conforms to the labelled amount. The obtained results also comply with USP <698> Deliverable Volume.

The microbial purity of the finished product complies with the acceptance criteria of Ph. Eur. 5.1.4 Microbial quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use for non-sterile dosage forms for cutaneous use. No preservative is necessary since the non-aqueous formulation contains paraffin liquid and plasticized hydrocarbon gel that do not support microbial growth.

Method of manufacture

Manufacturing formula for industrial batch size is described. The amount of gentamicin sulfate added is calculated based on the actual potency of the particular lot of gentamicin sulfate (measured by bioassay). Quantities of mometasone furoate and posaconazole to be charged are determined based on the assay of the active pharmaceutical ingredient lot(s) to be used.

The manufacturing process includes homogenisation steps, mixing and filling. Information on process parameters such as rotation speed, temperature and duration for each homogenisation process has been provided.

The process is considered to be a standard manufacturing process in accordance with the Guideline on process validation for finished products (EMA/CHMP/CVMP/QWP/BWP/70278/2012).

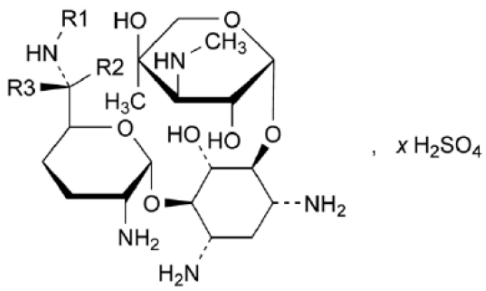
The manufacturing process of the finished product will be validated with 3 consecutive batches of the maximum commercial batch size prior to commercialisation. The validation scheme is presented and it is considered acceptable.

Intended holding times will be validated on commercial batches. Once the data for the holding time are available, an appropriate variation application will be submitted to update the dossier (e.g. under category F.II.b.3.h). Critical steps have been identified and in general appropriate in-process control (IPC) specification were established based on the applicant's experience with the manufacture of paraffin/plasticized hydrocarbon gel based suspensions and on the manufacturing process development work on two pilot and one industrial scale batches.

Control of starting materials

Active substance – Gentamicin sulfate

The chemical name of gentamicin sulfate is O-3-deoxy-4-C-methyl-3-(methylamino)-β-L-arabinopyranosyl-(1 →6)-O-[2,6-diamino-2,3,4,6,-tetradeoxy-α- D-erythro-hexopyranosyl-(1→4)]-2-deoxy-D-streptamine and has the following structure:



, $x\ H_2SO_4$

It is a white or almost white, hygroscopic powder. It is freely soluble in water, practically insoluble in ethanol (96 per cent). It is optically active.

The active substance exhibits stereoisomerism and has five main components including gentamicin

C1, gentamicin C2, gentamicin C1a, gentamicin C2a and gentamicin C2b. The composition of gentamicin is controlled routinely by HPLC and specific optical rotation.

Polymorphism has not been observed for gentamicin sulfate.

There is a monograph of gentamicin sulfate in the Ph. Eur. (0331), and the manufacturer of the active substance (gentamicin sulfate, non-micronised) has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for gentamicin sulfate, a copy of which has been provided within the application. It has been declared that materials of animal origin have been used for the manufacture of the active substance. A risk assessment with respect to viral safety of fish peptone used in the fermentation process of gentamicin has been conducted according to Ph. Eur. General text 5.1.7. It can be concluded that the risk of viral contamination in gentamicin is negligible.

The manufacturing process of the active substance (gentamicin sulfate, non-micronised) has not been addressed as all relevant aspects of the process have been evaluated by the EDQM prior to granting the CEP. Gentamicin sulfate, non-micronised is supplied to the applicant for micronisation. Information on the batch size and yield of gentamicin sulfate, micronised have been provided.

The characterisation of the active substance and its impurities have been addressed by the EDQM for gentamicin sulfate, non-micronised and by the applicant for gentamicin sulfate, micronised. There are no differences in the impurity profiles of non-micronised and micronised materials.

The active substance specification includes tests for description, identity (TLC, sulfates), appearance of solution/clarity and colour of solution (Ph. Eur.), pH value (Ph. Eur.), specific optical rotation (Ph. Eur.), composition (HPLC), related substances (HPLC), sulfate (titration), water (KF), assay (microbiological method), residue on ignition/sulphated ash (Ph. Eur.), microbiological contamination (Ph. Eur. 2.6.12), particle size (Ph. Eur. 2.6.12 - microscopy) and histamine content (LC/MS).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the VICH guidelines. Satisfactory information regarding the reference standards used for determination of assay, impurities and histamine have been presented.

Following micronisation, the active substance is repackaged in triple layer bags (PET, AL, PE (inner layer)). Documentation on the inner layer of the applicant’s active substance container has been provided.

Batch analysis data of 3 production scale batches of gentamicin sulfate, micronised have been provided. The results are within the specifications and consistent from batch to batch.

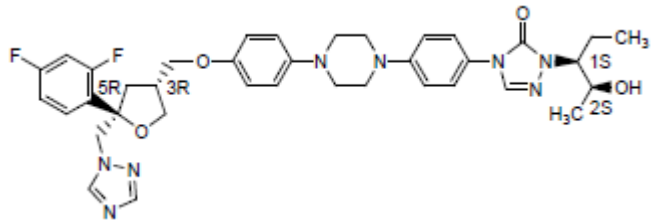
The stability results indicate that gentamicin sulfate, micronised manufactured by the proposed manufacturer is sufficiently stable. The stability results justify the proposed retest period of 48 months in triple layer bags (PET, AL, PE (inner layer)). The retest period is calculated from the manufacturing date of gentamicin sulfate, non-micronised.

Active substance – Posaconazole

The information on the active substance posaconazole is provided as full file.

General information

The chemical name of Posaconazole is 4-(4-{4-[4-({(3*R*,5*R*)-5-(2,4-Difluorophenyl)-5-[(1*H*-1,2,4-triazol-1-yl)methyl]tetrahydrofuran-3-l}methoxy) phenyl]piperazin-1-yl}phenyl)-2-[(2*S*,3*S*)-2-hydroxypentan -3-yl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one and has the following structure:



Molecular formula: $C_{37}H_{42}F_2N_8O_4$

Relative molecular mass: 700.79 g/mol

It is a white powder, which is practically insoluble in water but soluble in acetone, methanol and acetonitrile.

Posaconazole has 4 chiral centers, so 16 stereoisomers are possible. Posaconazole is the isomer with the stereochemical configuration of 3R, 5R, 1S, 2S. Of the sixteen possible stereoisomers, only six are considered to be probable. Chirality is controlled by two tests, specific optical rotation and chiral impurities by HPLC.

The drug substance is not considered hygroscopic.

Polymorphism: Posaconazole has 3 distinct polymorphs, designated as Form I, Form III, and Form IV. Form I is the polymorph consistently manufactured by the commercial manufacturing process. IR can distinguish between the polymorphs and the test is included in the active substance specification.

Posaconazole can exist in a monohydrate and in an anhydrous crystalline form (pseudomorphs). An amorphous content limit is proposed in the drug substance specification.

Posaconazole is used in the finished product as a micronised drug substance.

A flow diagram including both starting materials, intermediates, reagents, catalysts and solvents is presented in the dossier. Starting materials, intermediates and the active substance are presented as structural formulas reflecting stereochemistry. Raw material quantities, yields, batch sizes and process conditions are included as well. The batch size of the final active substance has been included in the description of the manufacturing process, including sufficient details on the micronisation step.

It is confirmed that recovered solvents are not used in the process. A low reprocessing rate is declared for compounds III, IV and the active substance, so reprocessing is not required to be defined and included in the description of the manufacturing process. Re-processing can be performed when the material (intermediate or final active substance) fail to meet a required specification.

Adequate in-process controls are applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. Certificates of analysis have been presented on starting materials and intermediates as justification for the proposed specification limits.

Two complex compounds, are proposed and have been appropriately justified as the designated starting materials.

Flow-charts of the complete route of synthesis of each proposed starting material have been presented in the dossier including solvents, catalysts etc. enumerated with regard to every step in the synthesis. The origin and fate of impurities which could be present in the designated starting materials have been discussed. Furthermore, information on all potential inorganic impurities as well as metal and solvent residues arising from the manufacture of each starting material has been

provided. For all impurities, detailed description on where in the process the impurities are introduced and removed has been presented. The control of the impurities including undesired stereoisomers has been justified, i.e. inclusion and exclusion of impurities in the specification.

An evaluation of the mutagenic potential of impurities in posaconazole drug substance according to the Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products EMA/CVMP/SWP/377245/2016 has been presented and found acceptable by CVMP.

The elemental impurity evaluation has been performed in line with the current ICH Q3D guideline. Batch data and a description of the analytical method used has been presented.

Specification, analytical procedures, reference standards, batch analysis and container closure

A specification is established by the finished product manufacturer for the active substance.

The active substance specification includes tests for: description, identity (IR, HPLC), specific optical rotation (Ph. Eur.), assay (HPLC), amorphous content (DSC), chiral impurities (HPLC), achiral impurities (HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction) and sulphated ash (Ph. Eur.).

All methods have been adequately validated and described according to VICH Topic GL1 (Validation: Definition) and GL2 (Validation: Methodology).

Satisfactory information regarding the reference standards used for assay and impurity testing has been presented.

Batch analysis results are provided for three batches of posaconazole manufactured at the proposed manufacturing site. Moreover, two certificates of analysis (CoAs) of micronised posaconazole batches from the releasing site Vet Pharma Friesoythe, Germany are provided.

The provided data show that all batches are very pure and data for specified impurities and residual solvent are far below the proposed limits.

Double Low-Density Polyethylene (LDPE) bags are the primary packaging material. Conformance to EU Regulation 10/2011 and subsequent amendments have been confirmed.

Stability

Stability data are presented for three stability batches of micronised posaconazole. Supportive data generated at other manufacturing sites are provided as well.

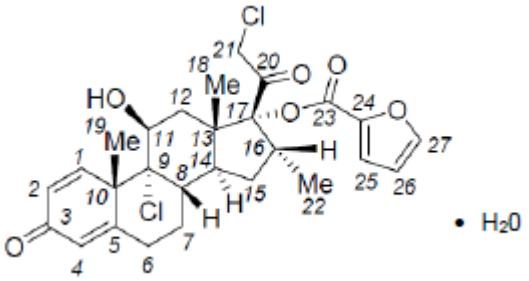
The proposed retest period of 36 months can be accepted for micronised posaconazole drug substance when stored below 30 °C and in original container.

Active substance - Mometasone furoate monohydrate

The information on the active substance is provided as full file.

General information

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



Molecular formula: $C_{27}H_{30}Cl_2O_6 \cdot H_2O$

Relative molecular mass: 539.45 g/mol

It is a white to off-white powder, which is practically insoluble in water, soluble in acetone and chloroform, slightly soluble in methanol, ethanol and isopropanol and freely soluble in tetrahydrofuran.

There are 8 asymmetric chiral centers of mometasone furoate monohydrate. The configuration of the active substance is controlled by optical rotation with the same limits as set in Ph. Eur. for the anhydrous mometasone furoate.

The drug substance is not hygroscopic.

Mometasone furoate can exist in a monohydrate and in an anhydrous crystalline form (pseudomorphs). Only one polymorph form has been observed.

Mometasone furoate monohydrate is used in the finished product as a micronised drug substance.

There is a monograph of mometasone furoate monohydrate in the Ph. Eur. (2858).

Manufacture, process controls and characterisation

Mometasone furoate monohydrate is synthesised using two starting materials. The synthesis is adequately described. The flow diagram includes both starting materials, intermediates, reagents, catalysts and solvents. Starting materials, intermediates and the active substance are presented as structural formulas reflecting stereochemistry. Raw material quantities, yields, batch sizes and process conditions are included as well.

A justification for how each proposed starting material is appropriate with respect of the synthesis of mometasone furoate monohydrate has been provided.

It is confirmed that recovered solvents are not used in the process. A low reprocessing rate is declared for the active substance so reprocessing is not required to be defined and included in the description of the manufacturing process.

Adequate in-process controls are applied during the synthesis.

The specifications and control methods for intermediate products, starting materials and reagents have been presented. Certificates of analysis are presented on starting materials and intermediates as justification for the proposed specification limits.

Impurity profiles of the starting materials have been presented (listing potential organic, inorganic and/or genotoxic impurities as well as metal and solvent residues arising from the manufacture). Furthermore, detailed information on the origin and fate of the impurities in the starting materials has been provided including where in the process the impurities are introduced and removed. The control of the impurities has been justified, i.e. inclusion and exclusion of impurities in the specification.

A satisfactory risk assessment on elemental impurities according to ICH Q3D has been performed on the active substance.

Potential and actual impurities were well discussed with regards to their origin and characterised. An evaluation of the mutagenic potential of impurities in mometasone furoate monohydrate drug substance according to the Guideline on assessment and control of DNA reactive (mutagenic) impurities in veterinary medicinal products EMA/CVMP/SWP/377245/2016 has not been presented. The justification provided was considered acceptable by CVMP.

Specification, analytical procedures, reference standards, batch analysis and container closure

A specification is established by the finished product manufacturer for the active substance. The active substance complies with the monograph in the Ph. Eur. (2858) and additional requirements for residual solvents, particle size distribution, anhydrous form content and microbiological limits.

The specification includes tests for: description, identity (IR, HPLC), specific optical rotation (Ph. Eur.), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), particle size distribution (laser diffraction), anhydrous form content (XRPD) and microbiological quality (Ph. Eur.).

All additional methods have been adequately validated and described according to VICH GL1 (Validation: Definition) and GL2 (Validation: Methodology).

Satisfactory information regarding the reference standards used for assay and impurity testing has been presented.

Batch analysis results and certificates of analysis are provided for three batches of mometasone furoate monohydrate micronised tested at the active substance manufacturer and for two batches tested at the releasing site Vet Pharma Friesoythe, Germany.

The provided data show that all batches are very pure and data for specified impurities and residual solvent are far below the proposed limits.

A triple layer Low-Density Polyethylene (LDPE) bag is the primary packaging material. The packaging material conforms to EU Regulation 10/2011 and subsequent amendments.

The LDPE bag containing the drug substance is placed into a secondary container (plastic drum).

Stability

Stability data are presented for three stability batches (micronised) including six months accelerated data (25 °C /60% RH) and 36 months long-term data (2 °C - 8 °C). The drug substance is stable, when stored in the proposed container closure system.

The proposed retest period of 36 months can be accepted for mometasone furoate monohydrate drug substance when stored at 2 °C - 8 °C in original container.

Photostability studies were performed in solution and solid state under VICH conditions. As significant degradation was observed, 'protect from light' is included as a storage condition.

Excipients

Paraffin liquid added to the process as base complies with Ph. Eur. monograph 0239. The applicant's specification for paraffin liquid includes additional requirements for four solvents.

The other excipient, plasticized hydrocarbon gel, is described in the dossier as solution of polyethylene in mineral oil

Plasticized hydrobarbon gel is a significant component of the formulation and its properties can directly affect the critical quality attributes. Plasticized hydrobarbon gel in-house specification has been appropriately justified and includes the following test parameters: description, texture, identification of two components, polyethylene content, consistency, acidity/ alkalinity, specific gravity, readily carbonizable substances and viscosity. The manufacturing process of plasticized hydrobarbon gel has been discussed. The name and address of the manufacturer of plasticized hydrobarbon gel are included in the dossier. Representative CoA are presented.

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

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

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

The excipients used to manufacture the finished product are not derived from materials of human or animal origin and therefore do not present any TSE risk.

The reaction components used to manufacture active substances gentamicin sulfate, mometasone furoate monohydrate and posaconazole are not derived from materials of human or animal origin, except for fish peptone used in the manufacture of gentamicin sulfate. TSE declaration for gentamicin sulfate issued by the active substance manufacturer is presented stating that the peptone is derived from non-TSE relevant fish.

Control tests on the finished product

The product specifications at release cover appropriate parameters for this dosage form, including appearance (by visual inspection), identity and assay of posaconazole (UPLC/UV), identity and assay of mometasone furoate (UPLC/UV), identity and assay of gentamicin (HPLC/microbiological titration), degradation products of posaconazole (UPLC-UV), degradation products of mometasone furoate (UPLC-UV), degradation products of gentamicin (HPLC/CAD), water content (KF), viscosity (Brookfield Viscometer), density 20 °C (Ph. Eur. 2.2.5), resuspendability, package observation (visual), particle size distribution (laser diffraction), morphology and agglomeration by optical microscopy (USP <776>), microbial quality (Ph. Eur. 2.6.12, 2.6.13) and filling volume (gravimetric).

The non-compendial analytical methods used for control of the finished product have been satisfactorily validated in line with VICH GL2 on validation of analytical methods. Validation reports are presented.

Batch analysis results for two pilot batches and one commercial scale batch are presented and show that the finished products meet the specifications proposed. Although, the analysed batches include 2% overage of mometasone furoate monohydrate, which will not be applied for future manufacture, they are considered representative of the finished product quality. CoA for three commercial batches, manufactured without 2% overage of mometasone furoate monohydrate, will be included in 3.2.P.4.5 when available.

Stability

Stability data of two pilot batches and one commercial scale batch of finished product stored under long term conditions (30 °C/65% RH, 30 °C/75% RH) for 24 months, accelerated conditions (40 °C/75% RH) for 12 months, refrigerated (5 °C) C for 24 months were provided. The bottles were placed in upright and inverted positions.

The stability batches have been manufactured with 2% manufacturing overage of mometasone furoate monohydrate. This overage will not be applied for commercial manufacture. Three commercial validation batches will be placed on stability when available. Since the assay of mometasone furoate monohydrate does not decrease significantly upon storage, the added overage is not expected to have an influence on stability conclusion. The submitted stability results obtained on the formulation with 2% overage of mometasone furoate monohydrate are considered predictive of stability of the formulation proposed for marketing (the formulation without overage).

Investigated parameters: appearance (visual), identification (ID) of posaconazole (UPLC/UV), ID of mometasone furoate (UPLC/UV), ID of gentamicin (microbiological titration), assay posaconazole (UPLC-UV), assay mometasone furoate (UPLC-UV), degradation products of posaconazole (UPLC-UV), degradation products of mometasone furoate (UPLC-UV), assay gentamicin (micro-biological titration), degradation products of gentamicin (HPLC/CAD), water content (KF), viscosity (Brookfield Viscometer), density 20 °C, resuspendability, package observation (visual), particle size distribution (laser diffraction), weight change (gravimetric), morphology and agglomeration by optical microscopy (USP <776>) and microbial quality (Ph. Eur. 2.6.12, 2.6.13). Acceptance criteria for the aforementioned test parameters are defined in the shelf-life specification of the finished product.

The specifications proposed at the end of shelf-life are the same as those proposed at release except for the test parameters degradation products of posaconazole and mometasone furoate, assay of gentamicin sulfate, viscosity and particle size distribution which have wider shelf-life limits in comparison to the release specifications. The differences between release and shelf-life specifications have been appropriately justified.

For long-term conditions, no out of specification results occurred during the investigated period and all the tested parameters were compliant with specifications. However, fluctuations in assay results, partially attributed to analytical method variation, were observed for all drug substances. For accelerated conditions, the investigated batches remained within the specifications. No significant change occurred at 5 °C and 40 °C. The investigated parameters remained more or less unchanged.

A shelf life of 24 months with no special storage conditions is proposed which is considered acceptable.

A photostability study according VICH GL5, Guideline on Stability Testing Photostability Testing of New Veterinary Drug Substances and Medicinal Products (Option 2) was conducted to investigate the effect of light exposure on the quality of the finished product. It was demonstrated that the finished product is not sensitive to light.

No impact on the quality of the finished product was observed during freeze and thaw studies.

No temperature precaution is required for this product.

The drug product is packaged in multi dose containers; therefore, an in-use stability study is performed. The shelf life after first opening of 3 months is proposed and considered acceptable. The in-use stability study has been performed with one fresh pilot scale batch. To simulate the product usage in different regions this study has been performed at 30 °C/65% RH and 30 °C/75% RH until the 3-month timepoint. The in-use study design has been justified. In addition, the in-use study will

be also conducted on one aged batch (near expiry date).

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the 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.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. No TSE safety risk has been identified.

As the manufacturing method is a relatively simple standard process and an acceptable process validation protocol for commercial scale batches was provided, it was accepted that full scale validation would be performed post-authorisation in accordance with the Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012). Process validation studies should be performed on the first 3 commercial batches. Should holding times be established during process validation on commercial scale batches, a variation should be submitted to register the updated manufacturing process.

In addition, the first 3 batches produced for commercial release should be placed in a stability study for which the protocol has already been approved. Any confirmed out of specification result, or significant negative trend, should be reported to the Agency.

Part 3 – Safety

Mometamax Ultra is an ear drops suspension containing a fixed combination of three active substances (gentamicin, posaconazole and mometasone) with antibiotic, antifungal and anti-inflammatory properties. It is indicated for topical treatment of canine otitis externa caused by bacteria (*Staphylococcus pseudintermedius*) susceptible to gentamicin and fungi (*Malassezia pachydermatis*) susceptible to posaconazole. The product is formulated for prolonged local pharmacological activity within the external ear canal.

Gentamicin is an aminoglycoside antibiotic with known activity against several bacterial pathogens; posaconazole is an antifungal azole exhibiting approximately 10-fold higher *in vitro* activity against *Malassezia* spp. when compared to clotrimazole, and in particular *M. pachydermatis*, commonly isolated from canine otitis externa; mometasone (mometasone furoate) is a synthetic corticosteroid with anti-inflammatory and anti-pruritic properties.

Safety documentation

A safety file in accordance with Article 12(3)(j) has been provided, which includes a pharmacokinetic and pharmacodynamic study, single-dose toxicity studies, a target animal safety study, and a user safety assessment. In addition, published scientific studies including summary reports from CVMP, CHMP and JECFA for each individual active substance are provided.

Pharmacodynamic, pharmacokinetic and target animal safety are discussed in detail in part 4.

No reproductive toxicity, including developmental toxicity, genotoxicity or carcinogenicity studies have been provided by the applicant.

Pharmacodynamics and pharmacokinetics

Please refer to part 4.

Toxicological studies

Proprietary toxicological studies are provided, together with supportive published scientific studies, including summary reports from CVMP, CHMP and JECFA for each individual active substance. Single-dose toxicity is further supported by two laboratory studies in rats. Repeat dose toxicity is further supported by the target animal safety study in puppies (see part 4).

No reproductive toxicity, including developmental toxicity, genotoxicity or carcinogenicity studies have been provided by the applicant.

Single dose toxicity

Two acute toxicity studies were carried out in rats, one investigating the dermal route of exposure and a second one investigating the oral route. In both studies, a test item containing all three active substances was used.

In a GLP-compliant single-dose dermal administration toxicity study in rats, 5 male and 5 female Sprague Dawley rats (226-244 g and 174-198 g, respectively) were administered a dose of 5000 mg/kg bw (approximately 10% of the body surface area) of test item. The study design was in accordance with OECD TG no. 402 for the testing of chemicals, entitled "Acute Dermal Toxicity: Fixed Dose Procedure". After dermal exposure in rats, results showed that acute toxicity of the test substance was low, i.e. no apparent toxicity was observed at up to 5000 mg/kg bw.

Acute toxicity was further assessed in a GLP-compliant single-dose oral study in rats. Five female Sprague Dawley rats (172-209g) received 2000 mg/kg of test item by oral gavage. The study design was in accordance with OECD TG no. 425 for the testing of chemicals, entitled "Acute Oral Toxicity – Up-and-Down Procedure (UDP)". After oral exposure in rats, results showed that acute toxicity of the test substance was low, i.e. no apparent toxicity was observed at up to 2000 mg/kg bw.

Repeat dose toxicity

In line with Directive 2009/9/EC, a repeat dose study in a single species is acceptable and can be replaced by a study conducted in the target animal. Repeat dose toxicity of the formulation has been assessed in the target animal safety study, which is discussed in detail in part 4. Published scientific studies, including summary reports from CVMP, CHMP and JECFA for each individual active substance, are provided supporting repeat dose via different routes of administration.

<u>Gentamicin</u>

Repeat dose parental and oral studies, ranging from 14 days to one year in rats, dogs and monkeys, are presented as a review.

Oral administration of 116 mg/kg bw/day of gentamicin for 90 days in rats was associated with soft stool. A 14-week oral study in dogs reported renal toxicity after dosing either 60 mg/kg bw/day for 60 days or 120 mg/kg bw/day for 30 days; a NOEL was set at 10 mg/kg bw/day. Diarrhoea and emesis was reported from all dose groups, including the lower dose group receiving 2 mg/kg bw/day. Studies investigating the intramuscular route of administration found increasing renal toxicity (dose dependant) starting from 10 mg/kg bw/day in rats and 3 mg/kg bw/day in dogs. In monkeys 50 mg/kg bw/day during 35 days via i.m. lead to cochlear hair cell loss and a reduction in the thickness of the sensory epithelium.

Mometasone furoate

The repeat dose toxicity of mometasone furoate is assessed from 10 studies performed in rats (oral route), mice (oral route), dogs (oral and intravenous) and rabbits (dermal route). A NOEL could not be derived from many of these studies as mometasone furoate caused commonly known glucocorticoid effects such as reduced food consumption and body weight, skin thinning (after topical administration in rabbits) and reduced splenic, adrenal and thymic weights. At higher doses, lymphoid atrophy in spleen, adrenals, thymus and lymphoid organs was noted.

Progestogenic effects were reported in rats and rabbits, but not in mice or dogs; such effects likely reflect the structural similarity between glucocorticoids and progesterone.

Rats were the most sensitive species and NOELs were set at 200 µg/kg bw/day in a 2-week study (corresponding to the lower dose group) and 5 µg/kg bw/day (corresponding to the mid-dose group) in a 1-month study. In the 1-month study in rats, effects in the higher dose group (receiving 125 µg/kg bw/day) were considered non-adverse and primarily consistent with glucocorticoid pharmacology.

Posaconazole

Posaconazole was well tolerated when administered daily to dogs by oral gavage for up to 12 months at doses up to 1 mg/kg bw/day; no behavioural effects were noted at doses of up to 30 mg/kg bw/day for up to 12 months. While pulmonary and neuronal phospholipidosis were observed, these are known effects following repeated administration of high doses of azole antifungals.

Tolerance in the target species of animal

Please refer to part 4

Reproductive toxicity

No reproductive or developmental studies have been conducted on the final formulation in dogs. Bibliographic studies, including summary reports from CVMP, CHMP and JECFA for each individual active substance, are provided.

Gentamicin

No effects on fertility, reproductive performance, or the development of offspring were observed in rats following an intramuscular injection of gentamicin at dose levels of up to 15 mg/kg bw/day for 70 days before mating (males) or from mating to 21 days post-partum (females). Intramuscular administration of gentamicin in rats at a dose level of 50 mg/kg bw/day for 6 days per week resulted in fetotoxicity (fetal death) but was not teratogenic. Likewise, subcutaneous administration

of gentamicin in mice at dose levels of 10 and 100 mg/kg bw/day resulted in fetotoxicity but was not teratogenic. Lastly, intramuscular administration of gentamicin in rabbits at dose levels of up to 4 mg/kg bw/day from gestation days 6 to 16 was not teratogenic.

Mometasone furoate

The studies listed were conducted in rat, mouse or rabbit. A NOEL of 2.5 µg/kg bw/day was derived from a teratology study in rats dosed via subcutaneous route, whereas the next dose level, corresponding to 15 µg/kg bw/day resulted in decreased pup bodyweights. At dose levels of 15 and 30 µg/kg bw/day, a dose-dependent decrease in maternal bodyweight was also observed. From a mouse teratology or embryo-fetal study, an oral NOEL of 20 µg/kg bw/day was derived, whilst mid and high dose groups (60 and 180 µg/kg bw/day, respectively) showed decreased maternal and pup bodyweight, cleft palate and decreased postnatal viability. At higher exposures in all studies referenced findings are prolonged gestation, dystocia, decreased postnatal viability, cleft palate, decreased pup and maternal bodyweight, delayed bone ossification, abortions, umbilical hernias and fetal malformations.

Posaconazole

Studies were conducted in rat and rabbit. A NOEL of 6 mg/kg bw/day was derived from an oral study in rat. At the mid and high dose levels of 18 and 36 mg/kg bw/day, respectively, prolonged gestation, dystocia, decreased live litter size, and decreased postnatal viability were observed. At the dose level of 36 mg/kg bw/day, decreased pup bodyweight was also observed.

Based on reproductive or developmental studies conducted in laboratory animals, the proposed summary of product characteristics states that the safety of the veterinary medicinal product has not been established during pregnancy and lactation. Studies to determine the effect on fertility in dogs have not been conducted. The product is not for use in breeding animals, and therefore the phrase "Do not use in breeding animals" is included in the SPC.

Genotoxicity

Several in vitro and *in vivo* genotoxicity studies are referenced from scientific literature, CVMP and JECFA reports.

Gentamicin gave positive results in some old inadequate in vitro mutagenicity tests, however, these findings could not be confirmed in a battery of well conducted genotoxicity tests (two in vitro tests (chromosomal aberration assay in CHO-K1 cells, a CHO/HGPRT gene mutation assay) and one in vivo mouse micronucleus test.

Overall it was concluded that gentamicin is unlikely to be genotoxic.

Mometasone furoate has been tested for gene mutation in bacteria, for chromosomal damage and gene mutation in a mouse lymphoma assay, and for chromosomal effects in an *in vivo* mouse bone marrow erythrocyte micronucleus assay and in a rat bone marrow clastogenic assay. All the studies showed mometasone furoate to be non-genotoxic. A Chinese hamster ovary cell study found dose-related simple chromosome aberrations but, since the doses tested were already at a cytotoxic level and the *in vivo* studies were negative, this finding is considered of limited relevance.

Posaconazole has been tested in bacterial gene mutation assays, Chinese hamster ovary cells, human peripheral blood lymphocytes and *in vivo* mouse micronucleus assay, all of which showed negative results.

Carcinogenicity

Based on the weight of evidence, gentamicin is unlikely to be carcinogenic which is substantiated by studies showing gentamicin is non-genotoxic; no pre-neoplastic lesions have been noted in repeated-dose studies; gentamicin does not contain structural features associated with carcinogenicity; other aminoglycosides were deemed not carcinogenic in rats.

Carcinogenicity studies conducted with mometasone furoate by inhalation in mice and rats revealed no observed carcinogenic effects of significance to humans. Specifically, only bladder/seminal vesicle mesenchymal tumours that commonly arise spontaneously in mice were seen.

Carcinogenicity studies conducted with posaconazole by oral administration in mice and rats revealed an increased incidence of adrenal cortical and medullary tumors in rats at the higher doses tested (30 mg/kg/day in male rats and 20 mg/kg/day in female rats). This is consistent with the known toxic effects on the adrenal glands of high, repeated exposure to azole antifungals.

No proprietary carcinogenicity data have been provided. This is acceptable since the three components of the product are characterised separately as being non-carcinogenic and non-genotoxic.

Studies of other effects

No specific studies on the immunotoxicity or neurotoxicity of the three active substances were provided. This is acceptable because no indications of such effects were observed in toxicology or pharmacodynamics studies.

Excipients

The final formulation contains paraffin liquid and plasticized hydrocarbon gel comprised of mineral oil and polyethylene. The excipients are found in otic dog products on the European market and various human medicinal products and are not considered to represent a safety concern.

User safety

A User Risk Assessment report was prepared based on the three guidelines published by EMA: Guideline on user safety of topically administered veterinary medicinal products EMA/CVMP/SWP/721059/2014, Guideline on user safety for pharmaceutical veterinary medicinal products EMEA/CVMP/543/2003-Rev.1 and Guideline on pharmaceutical fixed combination products EMEA/CVMP/83804/2005.

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of dermal, oral and ocular exposures. The exposure scenarios are correctly identified in the different phases of application but the volume of exposure needs further substantiation. The identified hazards to the users include systemic glucocorticoid adverse effects on fetal developmental toxicity associated with mometasone furoate, pulmonary and neuronal phospholipidosis associated with posaconazole and nephrotoxicity associated with gentamicin.

Although users may be exposed to Mometamax Ultra by the dermal and/or indirect oral routes of administration, no acute adverse effects are anticipated. The product is of low acute oral and dermal toxicity, is not a skin irritant or sensitizer, and is only slightly irritating to the eyes. As the product

may be slightly irritating to the eyes after accidental user exposure, appropriate risk mitigation measures are proposed: "In case of accidental eye contact, flush the eyes thoroughly with water for 15 minutes".

Margins of exposure are calculated by dividing the toxicological reference value (TRV; based on relevant NO(A)ELs) by the estimated user exposure. Combined dermal + hand-to-mouth oral user exposures to mometasone furoate are evaluated for each exposure scenario. The separate oral and dermal MOE for gentamicin and posaconazole are sufficiently large that there is no concern regarding the safety of the combined exposure. All MOEs for gentamicin and posaconazole were above 100. All MOEs for mometasone furoate were above 100 with one exception, the MOE for the post-application long-term child combined exposure scenario. As a risk mitigation, text to limit children's close contact with the treated dog in the following days after treatment, has been included in the SPC.

User safety is improved by restricting the administration of Mometamax Ultra to a veterinary professional (see section 4.9); thus restricting the risk to the adult and/or child dog owner to that associated with the dosing dog.

It is estimated that the potential for product dislodgement during or shortly after dosing is 38%, based on the average size of a small dog ear and the remaining excess amount of product when dosed according to the SPC. In the absence of an exact quantification, this is deemed as a conservative and qualified approach. The calculated MOE is above 100, and hence acceptable. The estimation of product slowly migrating from the treated ears post application is 25% resulting in the MOE for mometasone furoate being below 100. Therefore, the following risk mitigation measures are included in section 4.5: "Close contact between the dog and children should be limited in the days following the treatment due to unknown amount of the product possibly leaking from treated ear/s" and the following text in section 4.9: "Following dosing, the head should be restrained for approx. 2 minutes to prevent shaking and dislodging of product".

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided in accordance with the CVMP/VICH guidelines (VICH GL 6 and EMA/CVMP/ERA/418282/2005-Rev.1-Corr (2016)).

The environmental risk assessment can stop at Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing animal species.

Conclusions on the environmental risk assessment

An environmental risk assessment conducted in accordance with the relevant VICH and EMA guidelines has been provided. As Mometamax Ultra is intended for single use in dogs, a non-food producing animal species, the ERA can stop at Phase I and a Phase II assessment is not required.

Overall conclusions on the safety documentation

A safety file in accordance with Article 12(3)(j) has been provided. For conclusion on pharmacokinetic and pharmacodynamics please refer to part 4. Regarding toxicology, two single-dose rat studies investigating both the oral and the dermal routes of exposure, confirmed that short-term toxicity is not a concern.

The acute, sub-chronic and chronic toxicity for the three active substances target organs have been identified for oral and parenteral administration by median lethal dose studies and repeat dose studies in mice, rats, dogs and rabbits. Target organs have been identified and the most sensitive species and administration routes are identified in the search of suitable NO(A)EL values to base the toxicological reference values upon.

The applicant has provided a user risk assessment well composed and largely in accordance with the CVMP guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) and guideline on user safety for topically administered veterinary medicinal products (EMA/CVMP/543/03-Rev.1). The identification of the users, being the veterinarian administering the product and the adult and child dog owners coming into contact with the treated dog, is agreed. The exposure scenarios are correctly identified in the different phases of application and the quantitative exposure has been substantiated. The hazard identification is based on a review of studies on acute single-dose, repeat-dose, reproductive and developmental toxicity, genotoxicity and carcinogenicity. Identified hazards to the users are systemic glucocorticoid adverse effects, including foetal developmental toxicity imposed by mometasone furoate, pulmonary and neuronal phospholipidosis by posaconazole and nephrotoxicity by gentamicin. The references are publicly available assessment reports and original articles/reports for each of the studies. Three studies conducted by the applicant on skin and eye irritation and skin sensitization are in accordance to OECD test guidelines 404, 405 and 406. The formulation is classified as being slightly eye irritating, which is adequately addressed by a SPC warning in section 4.5. The total systemic exposure is calculated for mometasone furoate via extrapolation factors which is done according to guidelines, and to reach the human dermal NOEL three factors are applied. The calculated MOEs are all above 100 except for the long-term dermal exposure of a child via the possible close contact with a treated dog. Adequate risk mitigation measures are incorporated in the SPC.

Part 4 – Efficacy

The product Mometamax Ultra comprises a new fixed combination of three active substances, each of which has previously been authorised in veterinary medicinal products within the EU.

Accordingly, the applicant has provided a set of experimental data to support efficacy and target animal safety of the proposed product. Specifically, a total of nine new experimental studies were performed:

- Five *in vitro* microbiology studies (establishment of MIC values of gentamicin and posaconazole for field isolates of bacteria and fungi, documentation of non-interference between the 3 active compounds, assessment of co- and cross-resistance of bacterial isolates with high MIC values for gentamicin).
- Two *in vivo* laboratory studies in Beagle dogs (one pharmacokinetics study to generate PK/PD data for dose setting, and one study of product efficacy in an experimental in vivo model of canine otitis externa, to confirm the dose selected based on PK/PD considerations).
- One field study (combined safety and efficacy multi-centre field study performed at 35 different sites in France, Germany and the Netherlands, comprising a total of 316 client-owned dogs).
- One repeat-dose toxicity target animal safety study conducted in 3-month-old Beagle puppies, according to the target animal safety guideline (VICH GL43).

In addition to the 9 new experimental studies supporting efficacy and target animal safety of the product, the applicant has also submitted supportive scientific literature:

- On the pharmacology of the 3 active substances in the new product (gentamicin, posaconazole and mometasone).
- On resistance to the antimicrobial agents in the new product (gentamicin and posaconazole).
- On clinical management of canine otitis externa and clinical trials for therapeutics for canine otitis externaPharmacodynamics.

Mometamax Ultra otic suspension is intended for topical treatment of canine otitis externa caused by a mixed infection of bacteria and fungi pathogens susceptible to gentamicin and posaconazole, respectively. The product is formulated for prolonged local pharmacological activity within the external ear canal.

The antibiotic and antifungal compounds used in the product (gentamicin and posaconazole) were selected to target the bacteria (*Staphylococcus pseudintermedius*) and fungi (*Malassezia pachydermatis*) most commonly isolated from canine otitis externa clinical cases. Gentamicin is an aminoglycoside antibiotic accepted as having activity against bacterial pathogens commonly associated with otitis externa in dogs. Posaconazole is an azole antifungal exhibiting approximately 10-fold higher *in vitro* activity against *Malassezia spp*. than clotrimazole.

The steroidal agent mometasone furoate was added to alleviate inflammatory symptoms of otitis externa (pain, pruritus) and hence reduce self-inflicted trauma.

One *in vivo* GLP pharmacokinetic/pharmacodynamic 45 day depletion study, three *in vitro* minimum inhibitory concentration (MIC) studies, as well as several scientific publications were provided to describe the pharmacodynamic action/mode of action of the active substances.

The concentrations of all active compounds (gentamicin C1, gentamicin C1a, gentamicin C2, mometasone furorate and posaconazole) in ear wax and plasma samples were quantified using a single LC-MS/MS assay. While all active pharmaceutical ingredients are known to exhibit significant protein binding, the solvent extraction procedure used for preparation of ear wax samples allowed for quantification of free fraction concentrations.Consqently, the reported concentrations of the active compounds in plasma samples represented free (active) concentrations.

Local concentrations of active substances within the external ear followed similar kinetics: mean local concentrations declined by approximately 5-fold through the first 7 days post dosing, remained at a relatively plateau through days 7 to 30 post dosing, and declined to below detection levels through days 30 to 45 post dosing. At the plateau phase days 7 through 30, the mean local concentrations in the external ear were approx. 900 µg/g, 160 µg/g and 240 µg/g for gentamicin, mometasone and posaconazole, respectively.

From *in vitro* studies of gentamicin MIC values against a panel of relevant bacterial isolates, approximately 200 isolates of *Staphylococcus pseudintermedius* were examined representing both epidemiologically non-related canine otitis externa clinical isolates, collected through 2017-2020 in France, Germany, Hungary, Spain and the Netherlands, as well as clinical isolates collected during the pivotal field trial. In the same two studies, the maximal MIC value for posaconazole against a panel of *M. pachydermatis* isolates was 0.125 µg/ml. As such, the study is acknowledged to support the doses as used in the product.

An *in vitro* non-interference study of combinations of gentamicin, posaconazole and momentasone was provided. Non-interference between the three active substances in the product was assessed using clinical isolates from canine otitis externaof *Staphylococcus pseudintermedius*, *Pseudomonas*

aeruginosa, β-hemolytic *Streptococcus* species (representing *Streptococcus canis*), *E. coli* and *Malassezia pachydermatis* (5 isolates of each). Non-interference was tested using microdilution, with erythromycin included for assay quality control purposes. In general, no interference was found.

Based on the data provided, it has been shown that prolonged *in vivo* concentrations of the active substances in the product are present in the ear canal of young healthy Beagle dogs following label use, and *in vivo* antibiotic and antimycotic concentrations exceed MIC values for microorganisms associated with canine otitis media for at least 30 days. Although notable variability of the *in vivo* concentrations of the active substances were observed, the data package supports that systemic exposure of the active substances was low and both gentamicin and posaconazole concentrations in the ear remain above the MICs of the target pathogens for 30 days.

Development of resistance

Gentamicin is an aminoglycoside antibiotic, where resistance genes can be located on the chromosome, gene cassettes, plasmids, transposons or other mobile elements. The three main mechanisms of bacterial gentamicin resistance are known:

- Reduction of the intracellular concentration of the antimicrobial, either from reduced drug uptake (adaptive resistance) or active efflux mechanisms.
- Enzymatic modification of the drug, such as acetyltransferases (*AAC2′*, *AAC3* subclasses I, II, III, IV, and *AAC6′*), phosphotransferases (*APH2″*) and nucleotidyltransferases (*ANT2″*).
- Target site modification occurs via methyltransferases (*armA*, *rmtA*, *rmtB*, *rmtC*, *rmtD*, *rtmD2*, *rmtE*, *rmtF*, *rmtG*, and *npmA*).

Poor efficacy is expected for anaerobic bacteria and intracellular bacteria, and generally a degree of intrinsic resistance to aminoglycosides in enterococci and streptococci due to relative impermeability of their cell wall.

Posaconazole is a triazole (member of the azole antifungal agent). The most common mechanism of resistance to azoles in clinical isolates are alterations in lanosterol 14α-demethylase biosynthesis by mutations. Posaconazole resistance arises also either from mutations in the ERG11 gene encoding the CYP51 target enzyme or from the overexpression of efflux pumps.

Staphylococcus pseudintermedius could represent a concern for infections in humans, although dog ear infections are an uncommon source for such pathogens. *Malassezia pachydermatis* is considered a very rare cause of infections in human, only maybe in immunocompromised individuals.

Based on GLP-compliant *in vitro* MIC study, co- and cross-resistance were detected in several of the *Staphylococcus pseudintermedius* isolates from both the pivotal field study, as well as from a recent EU collection of epidemiologically unrelated, clinical isolates from dogs with otitis externa. Mobile genetic elements such as plasmids carrying multiple resistance genes are suspected based on the observed phenotypes.

A non-GLP *in vitro* study examined 'time-killing' curves of 3 epidemiologically unrelated bacterial species (*Staphylococcus (S.) pseudintermedius*, *Streptococcus (S.) canis (*β-haemolytic), *Pseudomonas (P.) aeruginosa* and *Escherichia (E.) coli*). Gentamicin demonstrated bactericidal activity against all isolates from 2-fold the MIC and higher (4x and 8x MIC), and within 4 hours of exposure at most concentrations. However, the applicant did not repeat the experiments at the gentamicin concentrations used in the product in order to demonstrate any added clinical benefit at these high concentrations (100 fold or more above the MIC).

The risk of resistance development with regard to the use of this product is considered relevant especially because low concentrations of active substances persist in the external ear canal for an unknown period of time. It is seen that there is a theoretical risk in exposing bacteria and fungi in the external ear to sub-MIC concentrations of antimicrobial agents. With the aim to reduce the risk, advice on the timing of external ear canal cleaning after the treatment has been added in the product information (in addition to standard warnings concerning use of antimicrobials). The risk mitigation measure was not included or assessed in the presented studies.

Pharmacokinetics

In the GLP-compliant study, the depletion of the three active pharmaceutical ingredients from the external ear canal for a period of 45 days after a single intra-aural administration at the therapeutic dose was characterised.

Six groups of 4 males and 4 female dogs (six to seven months old) received a single intra-aural administration of the test article at the therapeutic dose (1X) and were sampled for ear wax and blood on days 1, 7, 14, 21, 30, and 45 following treatment administration. Gentamicin (C1, C1a, C2/C2b), posaconazole, and mometasone furoate levels were measured. During the same period, dogs were also observed for a number of clinical parameters, including hearing assessment by a clap test (a person claps next to the dog positioned so that the dog cannot see or sense the clap). Once sampled, the predetermined set of animals for the given time point were removed from the study. The study design was in accordance with the guideline on the conduct of pharmacokinetic studies in target animal species (EMA/CVMP/EWP/133/1999).

All three active substances lead to detectable levels within ear wax samples after dosing. However, six of the ear wax samples from four different sampling points had negative weights. According to the applicant, the missing values did not significantly impact the integrity of the study. This is agreed.

Levels of all three active substances in ear wax samples depleted quickly, with 7.1% to 8.5% of the total dose (depending on the active substance) being retrieved on day 1 after dosing, and only 0.4% to 0.5% on day 7 after treatment. Elimination curves for all three active substances were similar. Despite the similar mean active substance concentrations found on days 14, 21, and 30 after dosing, the number of the 16 samples taken each time with concentrations below the limit of quantification (LOQ = 0.05 µg/g) increased over the sampling time points, being 0 until day 14 after treatment, 1-2 (depending on the active pharmaceutical ingredient) at day 21, 4-9 at day 30, and 11-14 at day 45 after treatment.

Plasma analyte concentrations depleted rapidly over time and were not quantifiable at most of the sampling time points. No quantifiable levels of mometasone furoate were found in any sampling point and no sample contained analytes above the limit of quantification (LOQ = 0.500 ng/ml) for any of the active substances from day 7 after treatment onwards (with the exception of 2 values considered spurious). Mean plasma concentrations detected on day 1 after dosing were as follows: posaconazole = 1.0 ng/ml (above LOQ in all 8 dogs); gentamicin = 2.8 ng/ml (above LOQ in 7 of 8 dogs). In light of the results, the sampling schedule was considered not optimal to match the T_{max} for all 3 active substances (i.e. only one 24-hour sample taken shortly after dosing). Therefore, no pharmacokinetic values were calculated from the plasma analyte concentrations for any of the 3 active substances.

Metabolism/Excretion

Information on metabolism and excretion of the three active substances were provided from published literature references.

Once systemically absorbed, gentamicin is not metabolised and is rapidly eliminated unchanged in the urine. Elimination of gentamicin depends on the kidney glomerular filtration rate.

Posaconazole is generally not metabolised and the vast majority is eliminated slowly unchanged in the faeces.

Mometasone furoate is primarily metabolised by cytochrome P450 3A4 in the liver into metabolites of which some are metabolically active. Mometasone and metabolites are mainly eliminated in the faeces.

Justification of fixed combination

A justification for the combination product, in accordance with the CVMP Guideline on pharmaceutical fixed combination products (EMEA/CVMP/83804/2005), was provided. Otitis externa is a multi-factorial condition, and for mixed infections, treatment success is generally regarded as requiring antibacterial, antifungal and anti-inflammatory components.

The main indirect benefit claimed for the combination is a single-administration dosage regimen by a veterinarian and a 28 to 42 day duration of the efficacy.

There is no known synergism nor antagonism between the three active substances, and other authorised veterinary medicinal products also include triple combination topical ear formulations (antibacterial, antifungal, anti-inflammatory). The guideline on pharmaceutical fixed combination products (EMA/CVMP/83804/2005-Rev.1) also requires that every active substance in a fixed combination product must be indicated at the moment of treatment assuch a combination should not be used to cover for a lack of appropriate diagnosis. In the pivotal field trial provided by the applicant, of the 316 dogs enrolled in the study, fungi were isolated from 118 dogs (37.3%) on study day 0, mixed infections with fungi and bacteria were found in 111 dogs (35.1%) and solely bacteria were isolated from 38 dogs (12.0%). From 48 cases (15.2%), no microorganisms could be cultured on study day 0. The applicant has specified that the product is only indicated for acute otitis externa caused by a mixed infection with both *Staphylococcus pseudintermedius* and *M. pachydermatis*.

Dose determination / justification studies

No studies were submitted to serve as dose determination/dose justification or pharmacokinetic (PK)/pharmacodynamic (PD) modelling simulations. Instead, the applicant refers to both *in vitro* (MIC studies, time-kill curves) and *in vivo* studies (PK/PD depletion study and target animal tolerance study) to demonstrate the relevance of the proposed dose with minimal absorption of the three active substances and ear wax concentrations well above the MIC for common pathogens during the majority of the treatment period.

It is noteworthy to consider that PK/PD relationships are typically used to justify dosages in well established infections and using validated approaches. Generally, it is acknowledged that PK/PD relationships provide a useful insight into clinical efficacy when plasma concentrations are considered as the target biophases and where appropriate established indices are available for sufficient drug/micro-organism exposure. Thus, for local infections, PK/PD aspects can only be considered as illustrative of a concentration at the infection site as a function of the MICs for the

targeted pathogens, without correlation to potential clinical efficacy.

For gentamicin, when C_{max} is considered as the index, a ratio of 8 to 10 is typically required to achieve optimal bactericidal activity; however, the magnitude of the same ratio for local infections is not established. From the PK/PD analysis provided by the applicant, for gentamicin, the C_{max}/MIC ratio is at least 100 till D 21. Also no information is known about the optimal C_{max}/MIC ratio for posaconazole against *Malassezia pachydermatis*. Consequently, such analysis could not be considered for this topical application. While in the field trial, a microbiological cure rate of 73.5 % was observed in 49 dogs presenting *Staphylococcus pseudintermedius* on day 0, a sufficient clinical cure rate (91.8%) was shown 28 days after treatment *i.e.* the bacterial overgrowth was sufficiently reduced by the treatment. Moreover, a sufficient cure rate of *Malassezia pachydermatis* was achieved in the field trial (81.1%, 77/95).

Dose confirmation studies

A GLP-compliant laboratory study was performed in 16 Beagle dogs. Otitis externa was induced using chemical disruption of epidermal integrity of the external ear canal of healthy dogs (croton oil instillation) followed by experimental topical inoculations of both ears with a cocktail of *Staphylococcus pseudintermedius* and *Malassezia pachydermatis* (characterised clinical isolates from South Africa) 3-4 h later.

Otitis externa was successfully induced in all animals, but was self-limiting and of relatively short duration (maximal clinical signs at day 3 after inoculation, returning to normal at approximately day 11). Three days after inoculation, 8 dogs were treated (group 2) according to recommendations (once with 0.8 ml of product instilled into each ear, after ear cleaning with a saline solution) and 8 dogs were left untreated and ear cleaning was not performed (group 1). Dogs were followed up for 11 days.

The microbiological cure rates against each pathogen on D3, D7 and D11 were the primary clinical endpoints. A statistically significant difference of the microbiological cure rate based on the worst ear was shown on D3 (0% versus 87.5% in group 1 and 2 respectively) and on D7 (14.3% versus 87.5% in group 1 and 2 respectively) for *M. pachydermatitis* (Fisher's exact test, two-sided, $p<0.05$).

In the beginning of the observation period, lower bacterial counts were observed in the treated group compared to the untreated group. The microbiological cure rates against *Staphylococcus pseudintermedius* were similar in both groups reaching 6/7 (85.7% in group 1) and 7/8 (87.5% in group 2). In treated animals, the severity of otitis externa as well as ear pain was reduced approximately 3-7 days post treatment, while untreated animals still exhibited ear pain and clinical signs. Clinical scores for otitis externa severity were reduced by approximately 2-fold in treated animals. The clinical cure (secondary endpoint) was significantly different (Fisher's exact test, two-sided, $p< 0.05$) on D3 (0% versus 75%), D4 (0% versus 87.5%) and D11 (42.9% versus 100%) in in group 1 and 2 respectively.

Target animal tolerance

Pivotal target animal safety study:

To support the target animal safety of the product, one pivotal 30-day GLP-compliant target animal safety study was conducted in 3-month old beagle puppies (4 males and 4 females for each dosing group) dosed on D1, D15 and D29 with 1X, 3X or 5X the recommended dose of 0.8 ml in each ear, once every other week for a total of 3 doses. The study was designed with reference to the guideline

on target animal safety for veterinary pharmaceutical products (EMEA/CVMP/VICH/393388/2006; VICH GL43).

Test article administration resulted in a mild eosinopenia in animals receiving 3X and 5X the recommended dose, an effect consistent with administration of the glucocorticoid component of the test article, mometasone furoate. Otherwise, there were no other differences in haematology and coagulation parameters on days 2 or 30. There were no test article related effects on urinalysis parameters on days 2 or 31/30 or in faecal colour and consistency on days 2 or 30.

On day 30, signs of chronic suppression of the adrenal glands were found in both sexes and on all parameters (weight, histology, cortisol release) at 5X the recommended dose; this is consistent with the effects of the glucocorticoid component of the test article, mometasone furoate. At 3X the recommended dose, consistent effects were seen in the female animals, whereas the male animals only showed significant changes regarding cortisol (basal as well as after ACTH-stimulation). At 1X the recommended dose, no statistically significant changes were seen, albeit the decrease in adrenal weight overall was found to be dose-dependent in the female animals. There was no other test article related effects on clinical chemistry parameters on days 2 or 30.

The test article related decreases in mean adrenal weights in males at 5X and females at $\geqslant$3X correlated microscopically with minimal to mild atrophy of the adrenal cortex. Minimal to mild atrophy of the epidermis of the external auditory canal and the epithelium lining the external surface of the tympanic membrane was seen in all three study groups, with no significant dose-effect.

Ototoxicity is a known risk associated with chronic use of gentamicin and histopathology was performed on the outer, middle and inner ear. There were no microscopic findings in the outer or inner sensory hair cells in the cochlear portion of the inner ear, and no microscopic findings in the middle ear, including the epithelium lining the tympanic cavity. Both epidermal/epithelial atrophy (of the epidermis of the external auditory canal and the external surface of the tympanic membrane) and adrenal cortical atrophy are known pharmacological effects of glucocorticoids and were attributed to the glucocorticoid component of the test article (mometasone furoate).

It is concluded that intra-aural administration of gentamicin – mometasone furoate – posaconazole otic suspension was generally well tolerated in Beagle puppies at dose levels of 1X, 3X, or 5X the therapeutic dose (1X = 0.8 ml/ear) administered once a week for a total of 3 doses.

The method chosen for administering extra doses in the 3X and 5X groups was inspired by the VICH GL43 guideline. However, the method chosen was also designed to mimic accidental overdoses (doses given once every other week for a total of 3 doses). Thus, animals may not have experienced precisely 3X, or 5X active substance concentrations over a 30 day study period which could explain the lack of a clear dose effect considering that the dose groups might have been exposed to similar concentrations, or the maximal effect was achieved already at 1X the recommended dose. However, known effects from the steroid component (mometasone furoate) confirm that animals were exposed to levels of active substance high enough to result in findings.

Local tolerance at the application site and ototoxicity:

Gentamicin is known to be related to ototoxicity and mometasone furoate can lead to mild atrophy of the epithelium lining the external surface of the tympanic membrane. Two of the submitted studies assessed hearing after single intra-aural administration of the final formulation at the therapeutic dose, i.e. the GLP-compliant pharmacokinetic and pharmacodynamic 45-day depletion study and the pivotal 30-day GLP-compliant target animal safety study. No objective hearing

assessments were performed in pivotal clinical trials. The dogs' hearing was assessed solely with a clap test (a person claps next to the dog positioned so that the dog cannot see or sense the clap).

The pharmacokinectic and pharmacodynamic depletion study revealed that the frequency of dogs responding to the clap test decreased markedly over time in the study. Specifically, the percentage of dogs responding on at least one ear decreased from above 85% prior to dosing to below 50% at all timepoints from day 21 after treatment onwards; and in the last groups of 8 dogs, i.e. dogs tested on day 45 after treatment, none of the dogs responded on any ear. It is noted though that 7 dogs out of 48 did not respond for any ear already before administration of the treatment and that a significant number of dogs (19/31) that did not react to the clap test at some time point reacted at a later time point.

In the target animal safety study , results revealed that seven dogs in the group treated with the test product did not respond on one or two ears to the clap test: fours dog on D16 and 3 other dogs on D30. The four dogs that did not respond at D 16, finally responded at D 30.

To conclude, the hearing 'clap' test performed in the two different studies revealed conflicting results. There is a lack of consistency in results between dogs and between studies. No adequate explanation could be provided. However, it was concluded that the clap test was considered a too insensitive method to assess hearing deficits related to gentamicin ototoxicity in very young dogs. This is due to a lack of specificity to distinguish deaf dogs from non-deaf dogs and due to the fact that gentamicin ototoxicity initially affects the high frequency hearing range, whereas the clap test mostly assesses the low frequency hearing range.

In addition, the applicant quoted two studies investigating otoxocity of gentamicin and performed in dogs with perforated tympanic membranes (Strain[1] et al. (1995) and Paterson[2] (2018)). In these two studies, no increased risk for ototoxicity have been observed. It is noted that the formulations are not comparable (aqueous solution versus oily solution).

The margin of safety related to ototoxicity was finally concluded as adequate, based on no abnormal inner ear histopathology results from the target animal safety study, the literature cited above and the lack of reporting of adverse events from the pivotal field trial.

Adequate SPC text has been added to reflect that gentamicin is a known ototoxic agent and no objective hearing tests were performed in the pivotal field trial.

Clinical field trials

One pivotal GCP, multicentre, positively controlled, randomised and partially blinded (because of difference in posology) clinical field trial investigated both the safety and efficacy of Mometamax Ultra for the initially proposed indications (i.e. treatment of otitis externa associated with strains of bacteria susceptible to gentamicin (*Staphylococcus pseudintermedius*, *Streptococcus canis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*) and fungi susceptible to posaconazole (*Malassezia pachydermatis*).

[1] Strain G.M., Merchant S.R., Neer T.M., Tedford B.L.,'Ototoxicity assessment of a gentamicin sulfate otic preparation in dogs', Am J Vet Res. 56(4), April 1995, p. 532-538. PMID: 7785834.

[2] Paterson S., 'Brainstem auditory evoked responses in 37 dogs with otitis media before and after topical therapy', J Small Anim Pract. 59(1), January 2018p. 10-15. PMID: 28718886.

A veterinary medicinal product authorised for the treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with *Staphylococcus pseudintermedius* and *Malassezia pachydermatis* containing florfenicol, terbinafine and betamethasone acetate was used as positive control.

Client-owned dogs aged at least 12 weeks and weighing more than 2.4 kg were enrolled on study day 0 if they presented clinical signs of otitis externa (Total Clinical Score (TCS) ≥ 5 of at least one ear, according to the OTIS-3 system of Nutall et al. (2014)). Dogs were not included if presenting a ruptured tympanic membrane, foreign body, mites, a severe illness, an endocrine disorder, another medication, occluded ear channels, an extended ear infection, chronic otitis that had been treated unsuccessfully before, hypersensitivity to one of the active ingredients or if pregnant or lactating. Cases with concomitant disease (*Sarcoptes* mites, otic mange, mucometra, gingivitis, atopic dermatitis) were removed from the per protocol (PP) population. A total of 316 client-owned dogs (investigated veterinary product, IVP: n=153, control product, CP: n=163) from 35 veterinary practices in France, Germany, and Netherlands were initially enrolled into the study. Two dogs enrolled from Netherlands, 25 dogs from Germany and 13 dogs from France were excluded from the PP population due to protocol deviations. A total of 276 dogs were retained in the PP population (IVP: n=143, CP: n=133). The dogs ranged from 2.4 to 80.7 kg in weight and were between 12 weeks and 15 years of age.

Of the 316 animals included, 258 (82%) had no history of otitis externa within the past 6 months. In total, 31 animals (10%) had an acute otitis, whilst 27 animals (9%) had a recurring otitis within the past 6 months. In both study groups, the mean ear score for the enrolled ear was slightly higher in the animals with a history of otitis in the past 6 months. Overall, 132 (41.8%) of the animals included presented with bilateral otitis (both ears score ≥5), and 184 (58.2%) presented with unilateral otitis (one ear scores ≥5, one ear scores < 5). In total, 98 animals (31.0%) presented with a clear unilateral otitis (one ear scores ≥5, one ear scores = 0).

The primary efficacy endpoint was the treatment success rate on study day 28 in the PP population, defined as the significant reduction of clinical signs of otitis externa (TCS) on study day 28 (TCS ≤ 3) after an intermediate treatment success on study day 14 (TCS of ≤ 4).

Non-inferiority was investigated using the risk difference with a level of significance of $\alpha = 0.025$ and a tolerated difference of $\delta = 0.15$. If the lower confidence limit was above -0.15, non-inferiority was concluded. Secondary efficacy criteria were "Intermediate treatment success on study day 14", "Relapse rate at study day 42", and "Microbiological cure rate at study day 28".

The non-inferiority of the IVP as compared to CP was shown in the full data set analysis (PP, IVP: 128/143 dogs = 89.5%; versus CP 116/133 = 87.2 %, p<0.0001, lower 97.5% lower CI limit: -0.059).

Mixed infections with *S. pseudintermedius* and *Malassezia pachydermatis* were present in 74 animals on study day 0 (PP population, IVP group: 33 dogs and CP group: 41 dogs). In these dogs, the intermediate treatment success on study day 14 was 100% in the IVP group versus 97.6% in the CP group. The treatment success on study day 28 was 100% in the IVP group versus 90.2% in the CP group. Non-inferiority of IVP as compared to the CP was demonstrated (p=0.0007, 97.5% lower CI=-0.0543) of the control group. One dog (3%) in the IVP group relapsed by day 42 and no dogs relapsed in the CP group.

There was no significant difference for the "Intermediate treatment success on study day 14" and the "Relapse rate at study day 42". The microbiological cure rates based on dogs that cultured positive on study day 0 for *Staphylococcus pseudintermedius* in the IVP group was 73.5% (36 of 49) and 90%

(45 of 50) for the CP group. For *Malassezia pachydermatis*, microbiological cure rates were 81.1% (77 of 95) for the IVP group and 83.8% (83 of 99) for the CP group.

Pre-study and post-treatment MIC distributions of the target pathogens isolated in this study were determined and discussed in the separate *Antimicrobial Risk Assessment Report* (see sub-section on 'Development of resistance'). This report also discusses the risk of transmission or emergence of resistant bacteria or fungi of the relevant target species.

The tolerance of the IVP was also studied in this trial; however, it did not include any hearing evaluation, as a secondary endpoint. A total of 51 adverse events (AEs) were reported with similar numbers in both groups. One serious, unrelated AE was seen in the IVP group (broken leg), while four serious AEs were recorded in the CP group (otitis, epileptic seizure, haemorrhagic gastroenteritis, mucometra). Two adverse events (serious head shaking on study days 0-1, and polydipsia on day 1) were reported as potentially related to treatment with the IVP.

Nine non-serious, unrelated otic AEs concerning the un-enrolled, untreated ears were observed in the IVP group (otitis externa, erythema, otic mange), as compared to six in the CP group. Three cases of non-serious dermal conditions were seen in the IVP group during the study (dermatitis, sarcoptic mange, superficial pyodermatitis), and assessed as unrelated (as opposed to one case of atopic dermatitis in the CP group). One case of conjunctivitis was recorded in one IVP dog, and another dog in the group had a corneal ulcer during the trial. The corresponding number in the CP group was 4 cases (conjunctivitis). Non-serious gastrointestinal signs (vomiting, gastritis, soft faeces) were seen in 4 IVP dogs and 6 CP dogs (diarrhoea, gastroenteritis, vomiting, constipation) and were considered unrelated to the study drugs. Other systemic AEs which were considered unrelated to treatment were two transient cases of tiredness/somnolence (one in each group, day 0 and 1, respectively).

The observed adverse reactions were not considered to be treatment-related and therefore not included in SPC section 4.6.

No blood, serum or urine samples were collected during the study. The applicant based this decision on the results of the tolerance studies, where it was concluded that glucocorticoid-related changes were not expected after single use of the product. However, the tolerance study was performed in healthy animals, while in this trial the product was applied in inflamed ears. Documentation of potential systemic effects of the IVP was not performed.

Results of this pivotal field trial demonstrated the non-inferiority of the proposed product over a positive control product.

Overall conclusion on efficacy

Pharmacodynamics:

Mometamax Ultra otic suspension is intended for topical treatment of acute canine otitis externa and contains three active substances, gentamicin, posaconazole, and mometasone furoate. The new fixed combination is justified by acknowledging the fact that otitis externa is a multi-factorial disease, caused by mixed infections, and by acknowledging that treatment is generally considered to require an antibacterial, antifungal and anti-inflammatory component. The antibiotic and antifungal compounds used in the product (gentamicin and posaconazole) were selected to target the bacteria (*Staphylococcus pseudintermedius*) and fungi (*Malassezia pachydermatis*) most commonly isolated from canine otitis externa.

One *in vivo* GLP pharmacokinetic/pharmacodynamic 45 day depletion study, three *in vitro* MIC studies, as well as several scientific publications were provided to describe the pharmacodynamic action/mode of action of the active substances.

Based on the data provided, it has been shown that prolonged *in vivo* concentrations of the active substances are present in the ear canal of young healthy Beagle dogs following label use, and *in vivo* antibiotic and antimycotic concentrations significantly exceed MIC values for target pathogens associated with canine otitis media for at least 30 days. For topical products, PK/PD aspects can only be considered as illustrative of a concentration at the infection site as a function of the MICs for the targeted pathogens, without correlation to potential clinical efficacy.

Resistance:

Based on one GLP-compliant *in vitro* MIC study, co- and cross-resistance were detected in many of the pathogenic bacterial isolates from both the pivotal field study, as well from a recent EU collection of epidemiologically unrelated, clinical isolates from dogs with otitis externa (*S. pseudintermedius*).

A non-GLP *in vitro* study examined 'time-killing' curves of three epidemiologically unrelated bacterial species (*Staphylococcus (S.) pseudintermedius*, *Streptococcus (S.) canis (*β-haemolytic), *Pseudomonas (P.) aeruginosa* and *Escherichia (E.) coli*). Gentamicin demonstrated bactericidal activity against all isolates from 2-fold the MIC and higher (4x and 8x MIC), and within 4 hours of exposure at the most at all concentrations.

With the aim to reduce the risk, advice on the timing of external ear canal cleaning after the treatment has been added in the product information (in addition to standard warnings concerning use of antimicrobials). The risk mitigation measure was not included or assessed in the presented studies.

Pharmacokinetics:

The majority of the dosed active pharmaceutical ingredients deplete quickly from the ear canals. Measurable concentrations of all three active substances were found within the ear canals of practically all dogs up to 21 days following dosing; after 30 days, approximately half the samples had concentrations below the lower limit of quantification and after 45 days, this characterised the majority of the samples. Systemically, very little amounts of the active substances were absorbed.

Dose determination:

No studies were submitted to serve as dose determination/dose justification or PK/PD modelling simulations.

Dose confirmation:

In support of the efficacy, a number of published references and a GLP-compliant laboratory study in 16 Beagle dogs were provided. In the dose confirmation study, otitis externa was induced with croton oil application followed by topical inoculations in both ears with *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*. Three days after inoculation, 8 dogs were treated with the IVP and 8 control dogs were left untreated. Microbiological cure rates against each pathogen in the most severely affected ear were the primary endpoint while the clinical cure was the secondary endpoint. A statistically significant difference of the microbiological cure rate was shown on day 3 and day 7 for *M. pachydermatitis*. In the beginning of the observation period lower bacterial counts were observed in the treated group compared to the control group. However, the microbiological cure rates against *Staphylococcus pseudointermedius* were similar in both groups reaching by day 11, 6/7 (85.7%) in group 1 and 7/8 (87.5%) in group 2. The clinical cure (secondary endpoint) was significantly different on days 3, 4 and 11 (at the end of the follow-up).

Tolerance:

The product is generally well-tolerated at the recommended dose.

In the 30-day repeated-dose study conducted in beagle dogs, skin atrophy within the ear canal was found in animals dosed three times with ⩾ 1X the planned therapeutic dose; and suppression of the adrenal glands plus mild eosinopenia were found in dogs dosed three times with ⩾ 3X the planned therapeutic dose. These findings likely reflect chronic effects of mometasone furoate locally (skin atrophy) and systemically (other findings).

The hearing 'clap' test performed in the two different studies revealed conflicting results. No adequate explanation could be provided. However, it was concluded that the clap test was a too insensitive method to assess hearing deficits related to gentamicin ototoxicity in very young dogs.

The margin of safety related to ototoxicity was finally concluded as adequate based on no abnormal inner ear histopathology results from the target animal safety study, literature, and the lack of reporting of adverse events from the pivotal field trial.

Adequate SPC text has been added to reflect that gentamicin is a known ototoxic agent and no objective hearing tests were performed in the pivotal field trial.

Efficacy:

One pivotal multicentre clinical field trial demonstrated that the product is non-inferior, compared to an authorised triple combination topical ear product, for the reduction of clinical signs of acute or acute recurrent otitis on study day 28, with mixed infections of *Staphylococcus pseudintermedius* and *Malassezia pachydermatis*, at the proposed dose.

Part 5 – Benefit-risk assessment

Introduction

Mometamax Ultra is an ear drops suspension containing a fixed combination of 3 active substances: gentamicin, posaconazole and mometasone furoate. The combination is considered a new fixed combination of active substances, each of which has previously been authorised within EU.

Gentamicin is an aminoglycoside bactericidal antibiotic which acts by inhibiting protein synthesis, posaconazole is a broad-spectrum triazole antifungal agent, whilst mometasone furoate is a corticosteroid with high topical potency. The product is intended for use in dogs for the 'Treatment of acute otitis externa and acute exacerbation of recurrent otitis externa associated with strains of bacteria susceptible to gentamicin (*Staphylococcus pseudintermedius*) and fungi susceptible to posaconazole (*Malassezia pachydermatis*)'. The recommended dose is 0.8 ml per infected ear.

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

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

Benefit assessment

Direct therapeutic benefit

The proposed fixed combination product contains three active substances with antibacterial, antifungal and anti-inflammatory activity. Combinations of such active substance classes are established treatment principles for the treatment of external ear infections in dogs. Current MIC surveys demonstrate continued susceptibility for common canine otitis pathogens against gentamicin and posaconazole.

The pivotal GCP-compliant clinical field trial demonstrated that the product is non-inferior, compared to an authorised triple combination topical ear product, for the reduction of clinical signs of acute or acute recurrent otitis, at the proposed dose.

The product is for topical use in the ear canal of dogs. Both gentamicin and posaconazole are concentration-dependent antimicrobials with high concentrations above the MIC of both active substances demonstrated in the ear canals of dogs for several weeks.

Additional benefits

The one-time administration of the product further minimises handling of the dog and facilitate owner's compliance.

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.

Risks for the target animal:

Administration of Mometmax Ultra in accordance with SPC recommendations is generally well tolerated.

However, gentamicin is a known ototoxic substance. The margin of safety related to ototoxicity was concluded as adequate based on no abnormal inner ear histopathology results from the target animal safety study, literature and the lack of reporting of adverse events from the pivotal field trial. Adequate SPC text has been added to reflect that gentamicin is a known ototoxic agent and no objective hearing tests were performed in the pivotal field trial.

Resistance:

The risk of resistance development with regard to the use of this product is considered relevant especially because low concentrations of active substances persist in the external ear canal for an unknown period of time. It is seen that there is a theoretical risk in exposing bacteria and fungi in the external ear to sub-MIC concentrations of antimicrobial agents and in this regard advice has been added to the product literature concerning correct timing of resuming ear cleaning practices after the effective treatment period.

Safety

Risk for the user:

The formulation is classified as being slightly eye irritating which is mitigated by a SPC warning. Long-term combined dermal and oral exposure of a child with mometasone furoate post application is below the MOE of 100 and a mitigation risk is stated in the SPC.

Risk for the environment:

Mometamax Ultra is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk management or mitigation measures

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

User safety:

User safety risks have been identified, mainly the risks associated with exposure via dermal and ocular contact. These risks are mitigated by precautionary text in the SPC.

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 strains of bacteria susceptible to gentamicin (*Staphylococcus pseudintermedius*, *Streptococcus canis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus mirabilis*) and fungi susceptible to posaconazole (*Malassezia pachydermatis*)".

Following evaluation of the data, the CVMP agreed to the following indication(s): "Treatment of acute otitis externa or acute exacerbation of recurrent otitis externa caused by mixed bacterial and fungal infections with *Staphylococcus pseudintermedius* susceptible to gentamicin and *Malassezia pachydermatis* susceptible to posaconazole."

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

Conclusion

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

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

Divergent position on a CVMP opinion for the granting of a marketing authorisation for Mometamax Ultra (EMEA/V/C/004987/0000)

We, the undersigned, have a divergent position to the outcome for the marketing authorisation of Mometamax Ultra.

Mometamax Ultra is an otic suspension containing a fixed combination of three active substances (gentamicin, posaconazole and mometasone). It is indicated for treatment of acute otitis externa and acute exacerbation of recurrent otitis externa caused by mixed infections of susceptible strains of bacteria sensitive to gentamicin (*Staphylococcus pseudintermedius)* and fungi sensitive to posaconazole (*Malassezia pachydermatis*). The product is formulated for prolonged local pharmacological activity within the external ear canal, for upto 30 days.

Aminoglycosides, like gentamicin are bacteriocidal, concentration-dependent antibiotics that are further recognized in both the WHO and OIE's list of critically important antibiotics. The bactericidal efficacy of aminoglycosides against bacteria is directly related to their peak concentration. Yet aminoglycosides have a narrow therapeutic index, and thus it is crucial to maintain or enhance their therapeutic efficacy while minimizing their side effects.

Mometamax Ultra represents the highest concentration for a single application of gentamicin in an otic veterinary medicinal product. Experiences with clinical use of gentamicin are that the ratio of the peak drug concentration to the minimum inhibitory concentration (MIC) of the bacterial pathogen or C_{max}/MIC is considered to be the parameter that best characterizes the *in-vivo* exposure of the pathogen to aminoglycoside concentrations. Optimal antibacterial activity for gentamicin is achieved when the peak concentration is 8 to 10 times greater than the MIC for the target pathogen (Kashuba *et al*. 1999 Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob. Agents Chemother*. **43**:623–9.). However, Mometamax Ultra represents gentamicin concentrations several hundreds of fold greater than the MIC_{90} for *Staphylococcus pseudintermedius*, for most of the treatment period. Also, using a formulation that maintains high gentamicin concentrations for most of the treatment period then applies a well known concentration-dependent antibiotic as a time-dependent dosing regimen, which is not a known property of gentamicin. No added clinical benefit could be demonstrated from the pivotal field trial, with this approach, in terms of microbiological cure rate or risk of selecting *S. pseudintermedius* isolates with elevated MICs, including gentamicin resistant *S. pseudintermedius* isolates, after the treatment period. This may also be due to other limitations of gentamicin in that efficacy is affected by changes in the local environment pH and oxygen-tension, or unable to kill bacteria with the ability to create biofilm or invade intracellularly (e.g. *Staphylococcus pseudintermedius*).

However, there could be an added potential for ototoxicity (cochleotoxicity; defined as hearing loss/impairment and/or vestibulotoxicity - balance disorders). Gentamicin is a well known ototoxic agent. The mechanism/s of aminoglycoside ototoxicity is not fully known but appears to involve both apoptotic (programmed cell death) pathways as well as formation of free radicals or through reduction of mitochondrial protein synthesis. In pathologic studies, aminoglycoside toxicity is associated with death of inner ear hair cells. Doses that are not enough to kill hair cells may damage their motion sensitive hairs (sterocilia), making them unable to respond to motion, at least for some months (Oei *et al*. 2004 Functional and anatomic alterations in the gentamicin-damaged vestibular system in the guinea pig. *Otol Neurotol* **25(1)**:57-64.).

Aminoglycoside-induced ototoxicity involving healthy animals does not necessarily represent the ototoxicity risk in clinical cases. Middle ear inflammation with/without bacterial lipopolysaccharides display increased cochlear uptake of aminoglycosides, and enhanced levels of cochleotoxicity without altered serum drug levels (Koo *et al*. 2015 Endotoxemia-mediated inflammation potentiates aminoglycoside-induced ototoxicity. *Sci. Transl. Med*. **7**:298ra118. doi:10.1126/scitranslmed.aac5546).

In laboratory dog studies for Mometamax Ultra, a 'clap test' was used to periodically assess hearing following product administration, with conflicting results. No hearing assessments were performed in the pivotal field trial. Exposure to loud sounds synergistically potentiates the ototoxicity of aminoglycosides, presumptively by the summation of reactive oxygen molecules generated by each insult alone (Jiang *et al*. 2017 Aminoglycoside-Induced Cochleotoxicity: A Review. *Front. Cell. Neurosci*. **11**:308. doi:10.3389/fncel.2017.00308). The synergistic ototoxicity of loud sounds and aminoglycosides is not confined to simultaneous exposure. Loud sound exposure prior to treatment with aminoglycosides can also potentiate aminoglycoside-induced hearing loss (Jiang et al. 2017).

While the risk of gentamicin ototoxicity is generally considered less via topical versus systemic routes of administration, topical (otic) induced ototoxicity is a well described phenomenon in both human medicine (Bath *et al*. 1999 Ototoxicity of Topical Gentamicin Preparations. *Laryngoscope* **109**:1088-1093.) and veterinary medicine (Ettinger's Textbook of Veterinary Internal Medicine, 8th Edition by Ettinger SJ, Feldman EC, and Cote E 2017 Elsevier Inc. ISBN: 9780323312110). Clinically, aminoglycoside drugs can enter the inner ear through systemic and topical pathways. In the systemic pathway, the drug passes through the blood-labyrinth barrier (BLB) and enters the inner ear through the *stria vascularis*. In topical administration, the drug can bypass the BLB into the middle ear and then through the round window membrane (RWM) into the inner ear (Fu *et al.* 2021 Mechanism and Prevention of Ototoxicity Induced by Aminoglycosides. *Front. Cell. Neurosci*. **15**:692762. doi:10.3389/fncel.2021.692762). The RWM in animals differs from humans as it does not contain the three layers seen in humans, and is thinner. Animal experiments have shown that the RWM contains micropinocytic vesicles (Kawabata I, Paparella MM 1971 Fine structure of the round window membrane. *Ann Otol Rhinol Laryngol* **80**:13-27.). Animal studies have also shown that substances with a molecular weight of less than 1000 (e.g. gentamicin, streptomycin, neomycin, and tetracycline) are transported actively through the RWM over a short period of time, with a slow excretion rate (Becvarovski Z 2004 Absorption of intratympanic topical antibiotics. *ENT-Ear, Nose & Throat Journal* **83**(Suppl 4):18-19.; Goycoolea *et al*. 1988 Experimental studies on round window structure: function and permeability. *Laryngoscope* **98**(suppl 44):1-20.). Moreover, the degree of ototoxicity from topical aminoglycosides appears to be directly related to the duration and dose of the preparation applied to the RWM (Smith BM, Myers MG. 1979 The penetration of gentamicin and neomycin into perilymph across the round window membrane. *Otolaryngol Head Neck Surg* 87:888-891.). Mometamax Ultra represents a VMP with a gentamicin concentration far above the optimal antibacterial activity and contained in a formulation that maintains those high concentrations, within the external ear canal, through most of the treatment period. Also during this treatment period, a potent steroid is included that can lead to thinning of the external ear canal epithelial lining and tympanic membrane.

The tympanic membrane consists of an outer layer of stratified squamous keratinized epithelium, a middle fibro-elastic connective tissue layer and an inner layer comprised of a cuboidal mucosal epithelium. Commonly-used drugs can diffuse across an intact tympanic membrane, albeit at a much lower concentration than present within the external ear canal. Pathologic damage of the tympanic membrane, without rupture, can increase drug diffusion (Veit *et al*. 2022 An Evaluation of the Drug Permeability Properties of Human Cadaveric *In Situ* Tympanic and Round Window Membranes. *Pharmaceuticals* **15**:1037. doi.org/10.3390/ph15091037). Also, a peptide-dependent active mechanism has been identified as capable of moving particles and/or molecules across an intact un-perforated infected tympanic membrane (Kurabi, A. *et al.* 2016 Discovery of a Biological Mechanism of Active Transport through the Tympanic Membrane to the Middle Ear. *Sci. Rep.* **6**, 22663). RWM absorption is enhanced with a ruptured tympanic

membrane. Middle ear infections increase the permeability of the round window to macromolecules, enabling penetration of pro-inflammatory signals and bacterial endotoxins (Kawauchi *et al*. 1989 Endotoxin permeability through the round window. *Acta Otolaryngol*. Suppl. 457:100–115. doi:10.3109/00016488809138892; Ikeda *et al*. 1990 Permeability of the round window membrane to middle-sized molecules in purulent otitis media. *Arch. Otolaryngol. Head Neck Surg*. **116**:57–60. doi: 10.1001/archotol.1990.01870010061018).

The tympanic membrane in dogs with otitis externa may be difficult to examine due to secondary changes of the external ear canal, pain associated with otoscopic examination, and accumulation of exudate, cerumen and debris. In dogs, clinical signs associated with middle ear disease (otitis media) are often similar to otitis externa. Significant otitis externa is commonly associated with otitis media; the tympanic membrane is ruptured in 25-50% of dogs with otitis externa, although 70% of dogs with otitis media had an intact tympanic membrane in one study (Ettinger's Textbook of Veterinary Internal Medicine, 8th Edition by Ettinger SJ, Feldman EC, and Cote E 2017 Elsevier Inc. ISBN: 9780323312110).

Thus, for the reasons and issues stated above, the undersigned have major concerns about benefit:risk of Mometamax Ultra for clinical use.

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