SCIENTIFIC DISCUSSION

1 SUMMARY OF THE DOSSIER

Easotic is an oily suspension for use in the ear, containing three active substances, namely hydrocortisone aceponate, miconazole and gentamicin. The Applicant for this veterinary medicinal product is Virbac, France. Easotic is used to treat dogs that suffer from acute or recurrent episodes of ear infections (otitis externa). It is given once a day for five days. The dose is 1 ml, which is given directly into the ear by one activation of the pump supplied with the bottle.

Hydrocortisone aceponate is a dermocorticoid with a high intrinsic glucocorticoid activity. Miconazole is an imidazole derivative, known for its antifungal potencies and gentamicin is an aminoglycoside antibiotic. Both compounds have been used for many years in human and veterinary medicinal products. Easotic contains a fixed combination ear drop suspension of these three active substances which have the following actions: antibacterial, antifungal and anti-inflammatory. These combined actions are of benefit in the treatment of external ear infections in the dog. The antibacterial and anti-fungal components allow the bacterial and fungal components of the disease to be addressed whereas the anti-inflammatory component reduces the swelling in the ear and more importantly provides the dog with pain relief. Within a short time period the dog will have less inflammation including less pain, giving greater comfort to the animal. This means that there will be both less scratching of and less damage to the ear canal. The most common side effects are mild to moderate redness of the ear.

The approved indication is: "Treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with bacteria susceptible to gentamicin and fungi susceptible to miconazole in particular *Malassezia pachydermatis*".

The pharmacovigilance system in place complies with the requirements in the guideline on monitoring of compliance with pharmacovigilance regulatory obligations and pharmacovigilance inspections for veterinary medicinal products in Volume 9 of the Rules governing medicinal products in the EU.

2. QUALITY ASSESSMENT

Composition

Easotic ear drops suspension for dogs contains three active substances: hydrocortisone aceponate (1.11 mg/ml), miconazole (as nitrate) (15.1 mg/ml) and gentamicin (as sulphate) (1505 IU/ ml) in a white suspension in a non-aqueous vehicle consisting of paraffin which complies with the Ph.Eur. The medicinal product is a suspension for administration into the ear canal.

Container

Easotic ear drop suspension is supplied in a multi-dose container with an airless pump. The suspension is dispensed in an airless white plastic bottle, which is composed of two extruded parts. A steel ball is added into the bottle to shake the suspension before first use. The bottle is closed with a 1 ml dosing pump equipped with a flexible canula. The pump is covered by a plastic cap to prevent accidental activation. The bottle is designed to deliver at least ten doses of 1 ml of product. Studies have been performed to establish the compatibility, safety and performance of the proposed packaging. Specifications including type of material, construction, quality specifications (routine tests) and procedures are provided. Statements that the packaging material complies with national and European food regulations (e.g. 2002/72/EC) are enclosed from the manufacturer. Satisfactory certificates of analyses are provided.

Clinical Trial Formula(e)

The clinical trial formula is the same as the final formulation. It was stored in a different plastic bottle made of polyethylene terephthalate (PET). The difference in containers are not considered critical as the dosing system is delivering 1 ml and stability studies performed in both containers have shown satisfactory results.

Development Pharmaceutics

The objective has been to develop a product to improve compliance and reduce dog handling with a posology expressed in ml instead of drops and to be administered less frequently (once a day instead of twice daily) and for a shorter duration than existing treatments (less than 7 days as a target). Information about compatibility between the ingredients in the formulation was provided at the request of the CVMP according to the EU guideline on Development Pharmaceutics for Veterinary preparations.

Active substances
The particle size distribution of active substances, which is identified as a critical parameter for the physical stability and the homogeneity of the product has been investigated. The sedimentation of miconazole was investigated by using two different particles sizes of miconazole nitrate. It appeared that the sedimentation slowed down with the lowest particle size and it was therefore chosen for the formulation.

Results from batch analysis and stability studies show that the particle size distribution are consistent and well within the set limits. It is thereby strongly indicated that the control of particle size for the active substances ensures satisfactory physical properties of the suspension. The homogeneity of the suspension has been checked by chemical dosage during the manufacturing process before, during and after the filling process. None of the active substances show any polymorphism.

Excipient
The choice of an oily vehicle has been decided according to the safety of the oil towards the skin and its established use in pharmaceutical, cosmetic and veterinary products. Moreover, the physical stability of the suspension is increased with the viscosity of the oil. Consequently, paraffin was chosen since it allows the product to be shaken before use and to keep the suspension homogeneous during the use. This is confirmed by validation and stability data presented.

The rheological properties of the paraffin chosen were not investigated. As the paraffin has a white appearance; it is not possible to check visually the sedimentation and the redispersibility. However, visually the sedimentation and the redispersibility have been checked with the assay of the active substances which allows the homogeneity of the finished product to be controlled.

Pharmaceutical form
The solubility of Hydrocortisone aceponate and Miconazole nitrate is low in aqueous and even in oily vehicles. Therefore, an oily suspension was chosen as a suitable pharmaceutical form. The choice of components is based on the concentration of the three active substances (gentamicin sulphate, miconazole nitrate, hydrocortisone aceponate) and the volume to be administered. Gentamicin sulphate and miconazole nitrate are well-known active substances described in the Ph.Eur., hydrocortisone acetate (or HCA) has more recently been approved in veterinary medicine through a Centralised Procedure, in Cortavance. The final concentrations of the three active substances are justified in relation to existing marketed products. Paraffin was chosen as the excipient of the formulation because it is compatible with the use on skin and it enables the chemical stability of the active substances.

Preservatives
The formulation does not contain any antimicrobial preservative. The product is a non-aqueous product which is not favourable to the microbial development and is self-preserving. Additionally, the

airless packaging does not allow the return of product or air into the bottle and therefore prevents any contamination of the product during its use over the short period of 5 days.

TSE
The active substances and the excipient included in the finished product are not derived from tissues or secretion of animals susceptible to transmissible spongiform encephalopathies. Therefore, the monograph 5.2.8 of the European Pharmacopoeia does not apply to these substances.

Packaging materials
The initial device of distribution of the product chosen originally was a mechanical pump. However, due to a deactivation of the pump when using it with the bottle upside down it was replaced by using an airless flexible pocket in replacement of the rigid PET bottles originally selected. The airless system makes it possible to use the pump without restriction of vertical positioning. All materials used for the bottle and pump comply with the European regulations. Water tightness of the bottle closed by 1 ml pump was checked and no sign of leakage was detectable.

Preliminary stability studies conducted in accelerated test conditions at 40°C for up to 6 months at the two extreme conditions of humidity (20%RH and 75%RH) recommended in the VICH GL3 guideline for Stability of New Veterinary Products show that although the packaging material is considered as semi-permeable, the external humidity conditions do not have a significant effect on the stability of the product.

Information about interactions between the container and the formulation (e.g. sorption and leaching) were provided at the request of the CVMP. The results prove the integrity of the plastic material. The stability of the primary packaging was confirmed, after its storage with pharmaceutical product. In conclusion, the results obtained for the interaction study performed on the pharmaceutical product conditioned in the primary packaging and stored for 6 months, did not reveal any diffusion from the plastic material into the pharmaceutical product. The compatibility between the primary packaging and the product is proven.

Dose reproducibility
The delivered doses were evaluated through 20 successive doses performed by different experimenters and pumps per experimenter. The test is performed according to Ph.Eur. 2.9.27 and is compliant.

Information about compatibility between the ingredients in the formulation was provided at the request of the CVMP. According to the EU guideline on Development pharmaceutics for veterinary preparations, preliminary stability studies can serve as a compatibility test. They have been performed and show good stability of each active substance in the suspension.

Method of Manufacture

The manufacturing formula is given for the commercial batch size. The manufacturing process is a standard process. A flow chart of the manufacturing process and in-process controls performed during the process was provided detailing the mixing of the actives and excipient and then filling and labelling. A description of the process is included in the dossier together with a description of the requirements for the in-process controls.

Information about testing frequency and requirements for all the in-process controls in the manufacturing process were provided. The in-process controls on the bulk are the mixing time and the appearance of the suspension. It is not necessary to perform other in-process controls on the bulk because the totality of controls are realised on the finished product. The in-process controls allow to check the conformity of each step and to ensure the production of a product in compliance with the finished product specifications. Results on the three validation batches showed that the manufacturing process leads to batches that meet the specification.

The process has been validated on three batches of industrial batch size. Validation is performed on pilot batches and production batches, as the manufacturing process is considered to be a standard

process the proposed batch range is acceptable. However, the applicant agreed that validation on each new scale-up will be performed prior to marketing.

Control of Starting Materials

Active Substances

Miconazole nitrate and gentamicin sulphate are described in the Ph.Eur. The documentation for both substances is provided as European Certificates of Suitability (CEP).

Miconazole nitrate
The quality of the substance is controlled by the current version of the monograph on Miconazole nitrate, supplemented by a limit for any other individually impurity, a test for residual solvent toluene and a test for residual boron, as mentioned in the Certificate of Suitability and completed with the test for particle size distribution.

The proposed limits for organic and inorganic impurities and residual solvents (toluene and ethanol) have been discussed in sufficient detail and are in line with relevant VICH guidelines. Batch data for three batches, are provided and all results are in accordance with the proposed limits in the Ph.Eur.specification.

A re-test period on 12 months in plastic bags with no specific precautions for storage was accepted. Stability studies were carried out on two industrial batches of miconazole nitrate (stored in commercial packaging) both placed in accelerated testing conditions and in long-term testing conditions. After 6 months storage at 40°C/75 % RH and after 12 months storage at 25°C/60% RH, the data indicate that all the physico-chemical characteristics were preserved. There was no increase of known or unknown impurities and the titre of miconazole nitrate remained stable. It can be concluded that miconazole nitrate is a stable drug substance.

Gentamicin sulphate
The quality of the substance is controlled by the current version of the monograph on Gentamicin sulphate supplemented by additional requirements for impurities as mentioned in the updated Certificate of Suitability provided and completed with the test for particle size distribution.

Production batch sizes of gentamicin sulphate and miconazole nitrate are described.. The production scale corresponds to batches used for batch analyses. Particle size is controlled for all active substances and polymorphism does not exist for any of the three active substances. Impurities have been investigated according to the transparency list in Ph.Eur. No inorganic impurities or residual solvents are used. Batch data for three batches are provided and all results are in accordance with the proposed limits in the Ph.Eur. specification.

A re-test period of 4 years with no specific precautions for storage was accepted based on data provided. The batch size of gentamicin sulphate used in stability studies is production batch size.

Hydrocortisone aceponate
Hydrocortisone aceponate is not described in the Ph.Eur. or any other pharmacopoeia and the full specification is provided. Satisfactory descriptions of the nomenclature, structural formula and molecular weight and identification steps are enclosed in the dossier. A detailed flow chart of the synthesis process is provided. During the purification steps, quality controls are performed on each intermediate according to the agreed specifications. Residual solvents are controlled within the specification. Except for optical rotation all tests from the Ph.Eur. monograph of Hydrocortisone are included in the specification. The proposed limits for solvents, reagents, auxiliaries and intermediates are considered to be justified and were also accepted during the approval for Cortavance.

Physico-chemical characteristics including appearance, solubility, pKa, Melting point, UV spectrum and specific optical rotation have been presented. Polymorphism has not been found. A HPLC method is used to determine the content of hydrocortisone aceponate and related substances and has been

validated with regard to specificity, stability of solution (24 hours), linearity, accuracy and precision (repeatability and intermediate precision). The method has also been validated as stability indicating. Peaks obtained under forced degradation conditions are well separated from each other. The GC method used to determine the residual solvents has been adequately validated also according to the VICH guidelines.

The proposed limits for organic impurities, catalyst and residual solvents have been discussed in sufficient detail and are in line with relevant VICH guidelines. All methods are sufficiently described, validated and well documented by tabulated and graphic data, chromatograms and statistical evaluations. Batch data for three batches are provided and all results are in accordance with the proposed limits in the active substance specification.

A re-test period of 12 months in the proposed packaging material with no specific precautions for storage was accepted. Three production batches have been stored at 25°C/60% RH and 30°C/65% RH for 12 months and at 40°C/75% RH for 6 months and no changes observed. Additionally, the particle size has been investigated on two other batches stored at 40°C/75% RH for 6 months and no changes observed.

Excipients

Paraffin complies with the latest edition of the French pharmacopoeia for Vaseline with an additional test for *polycyclic aromatic hydrocarbons* as described in the Ph.Eur. monograph for Paraffin, white soft. It is stated that the two monographs are very similar and the choice of the French Ph. was justified by adding the test for polycyclic aromatic hydrocarbons. A certificate of analysis is enclosed.

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

It is declared in accordance with the guideline on *Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* (EMEA/410/01) and Ph.Eur. monograph 5.2.8 that no starting materials which enter the composition of the finished product, or materials which are used during the manufacturing process fall within the scope of the guideline. Easotic complies with Directive 1999/104/EC and the current TSE guideline (EMEA/410/01-Rev. 2).

Control Tests on the Finished Product

The detailed release and shelf-life specifications were provided in the dossier for Easotic including tests for appearance, deliverable volume, density, particle size, and identification of the actives, assays, impurities and microbiological quality. The updated specification includes the addition of a test on uniformity of mass of delivered doses and an identification test for Gentamicin sulphate by HPLC/LSD and the tightening of the limits for impurities relative to miconazole nitrate. A test for Uniformity of mass of delivered doses from multidose containers was added to the finished product specification (Ph.Eur. 2.9.27) at the request of CVMP.

Relevant test parameters and methods are included and acceptance criteria are based on batch data as well as on stability data. All analytical methods have been satisfactory validated i.e. demonstrated to be specific, linear, accurate, precise and robust. The HPLC method for determination and identification of the active substance and determination of related substances has been satisfactorily validated in line with VICH requirements.The method for particle size distribution has been validated regarding repeatability, which shows acceptable RSD between replicate determinations.

The finished product specifications are in compliance with relevant VICH guidelines where the VICH GL11 guideline on Impurities in new veterinary medicinal products allows contents of individual unidentified degradation products up to 1.0% without qualification. No limits for degradation products are included at release. This is accepted in accordance with VICH GL39 guideline as it has been demonstrated by stability data that the active substances do not degrade during manufacture of the

finished product. The limits for degradation products originating from miconazole were amended in the shelf-life specification based on current batch data.

Batch data are provided for pilot scale batches used throughout development. All data comply with the specification and at the same time justify the proposed specification. The levels of degradation products are consistently low. Although, process validation has only partly been performed on production scale batches it is considered acceptable not to ask for further batch analyses as the applicant has agreed to validate each new scale-up prior to marketing.

Stability Tests on the Finished Product

Three pilot batches have been stored at 25ºC/60% RH for 18 months and at 40ºC/75% RH for 6 months in the commercial packaging. The studies will continue for 36 months at 25°C/60% RH. Stability studies have not been performed at low relative humidity as prescribed in the VICH GL3 stability guideline. No significant changes were observed compared to the proposed limits in the shelf-life specification. One batch has been stored at VICH light conditions. The samples have prior to testing been stored for 6 months at 25°C/60% RH. No changes were observed.

A shelf-life of 18 months with no special storage conditions is acceptable. It was accepted, that only larger scale batches will be put on stability. The first three consecutive larger production scale batches will be tested according to the approved stability protocol.

In-use Stability Tests
Two in-use studies have been performed one simulating 5 days use and the other simulating 10 days use. The in-use testing is performed at room temperature. Appearance, density, assay, degradation products and microbiological purity were all investigated and no significant changes observed. The results confirm an in-use shelf life of 10 days for the finished product stored in its commercial packaging.

OVERALL CONCLUSION ON QUALITY

The ear drop suspension contains three active substances hydrocortisone aceponate, miconazole nitrate and gentamicin sulphate in an oily formulation. The formulation is a simple non-aqueous suspension which besides the active substances only consists of paraffin as excipient. A non-aqueous suspension has been chosen because of the low solubilities of all active substances in aqueous solutions. Critical parameters have been identified as particle size distribution and homogeneity. The formulation was found to be self-preserving and therefore does not contain any preservatives. The development work is generally acceptable and in accordance with relevant EU guidelines.

The finished product is manufactured by Virbac SA in France. Satisfactory process validation data have been presented. However, further validation data have been requested.

The active substances miconazole nitrate and gentamicin sulphate are well-known substances both described in Ph.Eur. The documentation for these active substances are provided as European Certificates of Suitability (CEP). The CEP's are supplemented by additional requirements for particle sizes. Hydrocortisone aceponate (HCA) is not described in any pharmacopoeia and full documentation has been provided. HCA has recently been approved in another centralised procedure (Cortavance cutaneous spray, solution, developed by Virbac SA). The excipient paraffin complies with the requirements in the French Pharmacopoeia monograph for Vaseline supplemented by an additional requirement from the Ph.Eur. monograph of Paraffin, white soft. The choice of the monograph in the French Pharmacopoeia has been justified.

The ear drops suspension is packed in a white airless plastic multidose container with a 1 ml dosing pump. Packaging materials comply with Ph.Eur.

No starting materials which enter the composition of the finished product, or materials which are used during the manufacturing process fall within the scope of Ph. Eur. 5.2.8.

The finished product specification is in accordance with Ph.Eur. and relevant guidelines.

Stability studies have been performed on each of the three active substances. All substances seem to be very stable and retest periods of 12 months have been accepted for HCA and miconazole nitrate, while a retest period on 4 years has been accepted for gentamicin sulphate. Stability studies have been performed on 3 pilot batches of the finished product at VICH conditions for 18 months. No significant changes have been observed at any of the investigated storage conditions. In-use stability testing and photostability testing does not reveal any significant changes in stability. A shelf-life of 18 months and an in-use shelf-life of 10 days are acceptable.

3. SAFETY ASSESSMENT

Pharmacokinetics

Gentamicin

Gentamicin is not absorbed after oral administration. Following subcutaneous or intramuscular administration, the peak plasma concentration is obtained between 30 and 90 minutes. Gentamicin is distributed into the extracellular space with minimal penetration into tissues other than the kidneys and the inner ear, due to active transport.

Transdermal absorption of gentamicin is considered negligible. This was demonstrated by a number of studies. The applicant provided a non-GLP *in vitro* study to determine the quantity of gentamicin which would cross the skin after cutaneous permeation of Easotic through canine ear fragments using a microbiological agar diffusion method. The result confirmed that transdermal absorption of gentamicin is extremely low (a maximum of 0.3% of the applied dose) even after 48 hours of incubation.

Transdermal absorption of gentamicin was also studied in another GLP-compliant *in vitro* study using the Franz-type diffusion cells model. Skin from the inner part of dog's ears (six donors) was used. Easotic was applied onto the external part of the epidermis. The results indicated that after 48 hours of application, only small amounts (2.2%) of the applied dose of gentamicin were found in the receptor liquid, reflecting a low cutaneous bioavailability.

In two further GLP compliant studies, the applicant investigated the persistence of gentamicin (and miconazole) after auricular instillation of Easotic in order to evaluate the duration required for the substance levels to drop below the MIC of the main pathogens responsible for otitis in dogs. Healthy young beagle dogs were treated in both ears for 5 consecutive days with 1 ml of Easotic. Due to large variations between dogs, no definite conclusions could be drawn. However, 45 days after the end of treatment, i.e. at 7 weeks, gentamicin concentrations in the ear canal were in most cases below the limit of quantification and in all cases below the MIC_{90} of the most susceptible bacterial species, *Staphylococcus spp*. (MIC_{90} = 0.5µg/ml).

Miconazole

The pharmacokinetics of miconazole was described in different species (rabbit, rat, dog and human) for different routes of administration. Following oral administration, bioavailability is low. In humans, the majority of an oral dose is directly excreted via faeces (about 50%) and about 10-20% in urine, as metabolites, within 6 days. When topically applied, there is little absorption of miconazole nitrate through the skin or the mucous membranes. Transdermal absorption of miconazole is considered negligible.

In two GLP compliant studies, the applicant investigated the persistence of miconazole (and gentamicin) after auricular instillation of Easotic in order to evaluate the duration required for the substance levels to drop below the MIC of the main pathogens responsible for otitis in dogs. Healthy young beagle dogs were treated in both ears for 5 consecutive days with 1 ml of Easotic. The results showed that at ten days after the end of treatment (Day 14), miconazole concentration of at least

1.4 µg/ml was present in all ear canals. However, 24 days after the end of treatment, miconazole was not detected in the external ear canal of any dog.

Hydrocortisone aceponate (HCA)
In several laboratory species (rats, rabbits, guinea pigs) transdermal absorption of hydrocortisone aceponate was demonstrated and appears low. Highest concentrations were found in the gastro-intestinal tract followed by the liver and kidneys. Unchanged hydrocortisone aceponate was not detected in the urine or faeces following topical application but was detected in the urine following subcutaneous administration. A higher proportion of the dose was eliminated in faeces rather than urine. In a study in rabbits, no difference was seen in plasma pharmacokinetics following a single topical application of hydrocortisone aceponate to intact or scarified skin.

In dogs, three GLP-compliant dermal absorption studies using radiolabelled HCA topically on clipped intact skin at a dose slightly lower than the one recommended for Easotic were conducted. Results show that HCA and/or its metabolites are absorbed in the systemic circulation and are measurable from 4 hours after the first dose with an increase at least up until 48 hours (the end of observation) after a single administration. After repeated doses, C_{max} is seen after 414 hours (~10 days after last application) and the estimated half-time was 267 hours. It thus appears that continued absorption and prolonged systemic exposure can take place on intact (dermal) skin.

In healthy dogs, two studies were presented investigating the pharmacokinetics of HCA in the auricular canal in dogs at a dosing regimen similar to the one recommended for Easotic (1.09 mg HCA/ml per ear for 5 days). After daily administration for 5 days, C_{max} was reached after approximately 160 hours. The terminal half-life in males was approximately 160 hours. Thus, some absorption of HCA can be expected when using Easotic according to recommendations. Systemic bioavailability was estimated with approximately 10%. Radioactivity was mainly found in the dermis and hypodermis of the skin and the accumulation observed 4 hours following last treatments was insignificant after two more days.

Possible differences in the pharmacokinetics between healthy dogs and dogs with otitis externa may be due to the presence of cerumen, exudates and/or biofilm present in the external auricular canal. In cases of exudate or cerumen, skin resorption might be reduced. However, in the case of inflammatory disease (e.g. external otitis), resorption would be expected to increase. The clinical impact is unknown, but is not expected to be significant considering the results of tolerance and clinical studies.

Toxicological studies

Single dose toxicity

Gentamicin
Gentamicin was tested for acute toxicity by the intravenous, intraperitoneal, intramuscular and oral routes in a number of laboratory species. Low oral toxicity was seen following oral administration, which is associated with low oral bioavailability. The greatest amount of data was available for intramuscular administration and this revealed a similar level of toxicity across the various species tested.

Miconazole
Miconazole was tested in single dose toxicity studies the by oral, intraperitoneal, intravenous, and subcutaneous routes in a number of laboratory species. Following oral administration miconazole induced low acute toxicity with LD_{50} >160 $mg.kg^{-1}$ in the dog. However, large interspecies differences were seen.

Hydrocortisone aceponate (HCA)
Acute toxicity data show that hydrocortisone aceponate induced a variety of toxicity symptoms including sedation, ataxia, dyspnoea, cyanosis, mydriasis, lachrymal secretion, muscular hypotonia, decreased food consumption and decreased bodyweight gain, vomiting and death. However, following oral administration no acute toxic effects were observed at 1000mg/kg in rats and mice or at

8000mg/kg in dogs. Following intraperitoneal administration no acute toxic effects were seen at 464 mg/kg in rats and mice or at 100 mg/kg in dogs. Following subcutaneous administration no acute toxic effects were seen at 464 mg/kg in rats or at 681 mg/kg in mice and dogs. Following dermal administration no acute toxic effects were seen at the highest dose tested (4000mg/kg) in rats and mice.

Combination product Easotic
GLP studies were performed according to the relevant OECD guidelines. The objective was to allow GHS classification and to better identify the potential risk for the user in case of accidental exposure.

No mortality was seen following oral administration (LD_{50} > 5000mg.kg^{-1}) or dermal administration (LD_{50} > 2000mg.kg^{-1}) in the rat. The only observed effect was a slight piloerection in orally treated rats. The GHS classification was considered to be category 5 or unclassified. These results confirmed both the low toxicity profiles obtained for the active substances and their low oral and/or dermal bioavailability. Dermal and ocular irritation studies in the rabbit demonstrate the product to be non irritant to the skin and weakly irritant to the eyes. Precautions should be taken in the use of the product in order to limit eye contact for both the dog and the user.

Repeat dose toxicity
Repeat dose toxicity data were provided for at least two species for each of the three active substances (HCA: rat and rabbit; miconazole: rat and dog; gentamicin: rat, rabbit, dog & monkey). Furthermore, they include the cutaneous route (except for miconazole), which is the expected therapeutic route.

Gentamicin
Gentamicin has been tested in numerous subchronic and chronic toxicity studies in rats, dogs and monkeys. The intramuscular route was the most commonly used route, but the drug was also tested using oral and subcutaneous applications. After two weeks of daily intramuscular administration to rats, the NOEL was found to be 10 mg/kg b.w. After oral administration for 13/14 weeks the NOEL was determined to be 10 mg/kg b.w. in the rat and 10 mg/kg b.w. in the dog. The main effects seen related to the kidneys and internal ear, which are the target organs for gentamicin toxicity (the published CVMP Summary Report for gentamicin provides additional data relating to toxicity to these target organs). The results of the studies are broadly in line with those published in the CVMP Summary Report for gentamicin, which reports a NOEL for oral toxicity in the rat of 19 mg/kg b.w. from a 3 month study, and a NOEL for oral toxicity in the dog of 10 mg/kg b.w. as described above.

Miconazole
Miconazole has been tested for subacute toxicity in rats (10 days of daily dosing by the oral route) and chronic toxicity in both rats and dogs (26 weeks of oral dosing). The studies are rather old but the protocols were of acceptable quality and allowed chronic toxicity of miconazole to be addressed in a rodent and non-rodent species, using the most appropriate route when considering the bioavailability of this drug. In the subacute toxicity study, the NOELs were 10 mg/kg (females) and 30 mg/kg (males). At higher doses liver enlargement was observed (adaptive response to the drug metabolising enzyme inducing potency). In the chronic studies, the NOELs were 3 mg/kg for rats and 10 mg/kg for dogs. In dogs, the only observed effect was increased liver weight associated with the drug metabolising enzyme inducing potency of miconazole.

Hydrocortisone aceponate (HCA)
A number of GLP compliant repeated dose toxicity studies from the early 1980s have been provided. These include two subacute 13 week toxicity studies performed in rabbits with drug administration into the conjunctival sac and six chronic toxicity studies performed in rats and rabbits with daily administration (cutaneous or subcutaneous) for 26 weeks. Vehicles used for these studies included aqueous hydroxypropylmethylcellulose gel, cream and ointment.

Signs of toxicity seen, reflect the glucocorticoid activity of the substance. The principal organs of toxicity were stomach, lungs, spleen, thymus, adrenals, pituitary, kidney and liver. Subconjunctival administration was the most sensitive route tested with a NOEL of 0.13 mg HCA per day (in hydrophilic cream) in rabbits and rats. Subcutaneous and cutaneous administration resulted in similar

NOELs (0.33 mg and 0.32 mg hydrocortisone aceponate per kg bodyweight per day, respectively, in rabbits). At doses above the NOEL, chronic toxicity was weaker by the cutaneous route compared to the subcutaneous route. No difference in NOEL was recorded for abraded or intact skin.

Repeated dose toxicity studies did not use the vehicle used in the final product. However, given that the studies used the subcutaneous route as well as the intended cutaneous route, differences that may result from an altered absorption profile associated with the formulated product are considered to be adequately controlled for. Furthermore, given that the user safety assessment results in margins of safety greater than 10, any bias introduced as a result of the vehicle will be adequately controlled for.

Reproductive toxicity, including teratogenicity

According to Annex I of Directive 2001/82/EC as amended by 2004/28/EC, there is no requirement to conduct studies on the effects on reproductive toxicity when the systemic absorption of a topical treatment is negligible. However, although plasma concentrations curves appear to confirm a low bioavailability, the pharmacodynamic and pharmacokinetic data do not specifically quantify bioavailability.

Gentamicin
The reproductive toxicity of gentamicin was documented bibliographically. No evidence of reproductive toxicity was observed in rats after administration by the intramuscular route at doses up to 15 mg/kg b.w. In three studies performed with administration by the intramuscular route (rats) or subcutaneous route (mice), gentamicin was embryotoxic but without teratogenic potency. Consequently, this drug is contraindicated for use in pregnant women.

Miconazole
The reproductive toxicity of miconazole was documented bibliographically. The substance was tested for reproductive toxicity and embryotoxicity/foetotoxicity in rats and rabbits. The studies were not performed according to the GLP but protocols were of acceptable standards and in compliance with more recent OECD guidelines. In the rat reproductive study miconazole had no impact on fertility, gestation period, perinatal or postnatal performance. In both the rat and the rabbit miconazole has no teratogenic effects on foetuses or offspring. In both species malformations observed at the highest dose group of 100 mg/kg b.w. were associated with maternal toxicity.

Hydrocortisone aceponate (HCA)
Four studies were provided and all of which used the subcutaneous route. These assessed the impact of HCA on male and female fertility and on female maternal behaviour in the rat, on the critical period of organogenesis in pregnant rat and rabbit, and on peri- and post-natal development in rat.

Although OECD guidelines were not available when the studies were performed, the studies are considered to comply with the relevant OECD guidelines sufficiently and so are acceptable. The subcutaneous route was used because of good bioavailability when compared to the cutaneous route, or to the oral route (lowered bioavaibility due to intestinal esterases).

In the fertility study, a bodyweight decrease was the only effect seen parent males treated with 3 mg/kg b.w. At the highest dose (9 mg/kg b.w.), male and female bodyweights decreased, motor activity in females was inhibited during the lactating period and food consumption in females was decreased during the treatment period. Effects on the offspring were seen at 9 mg/kg b.w. Post-natal development showed a significant decrease in pup bodyweight after 2 and 3 weeks of lactation. Post-implantation losses increased. No signs of teratogenicity were recorded.

In two other studies, pregnant rats or rabbits were treated with HCA during their respective critical periods of organogenesis. Effects on food consumption and bodyweight gain were observed in parents. At high dosages (9 and 27 mg/kg b.w.) the number of foetuses decreased, post-implantation losses increased and foetus malformations increased. As for the chronic toxicity studies, the rabbit was by far the more sensitive species for all these effects.

In the peri- and postnatal study, the highest dose-level tested (27 mg/kg b.w.) produced maternal toxicity (inhibition of activity, mortality, decreased bodyweight and food consumption) and reduced weights of surviving offspring during the lactation period. However, duration of pregnancy was not influenced, all animals had a normal delivery and no teratological or embryotoxic effects were noted.

The lowest NOEL observed for reproductive toxicity in laboratory animals was seen in the rabbit following administration during organogenesis. The malformations observed are typical in type and localisation of those seen after administration of glucocorticoids including hydrocortisone in laboratory animals. Embryotoxicity were observed in offspring at doses from 0.33 mg/kg b.w. HCA with the subcutaneous route in rabbit, the most sensitive species. Similar values were obtained for the hydrocortisone base compound (0.48 mg/kg) *per* ocular route.

In summary, embryotoxic and teratogenic effects of HCA including skeletal changes, reduction in foetal and placental weight and elevated post-implantation losses, were seen in rats and rabbits at higher doses. No effects were seen on the length of gestation in either species. A reduction in the survival of the resulting offspring was observed. The lowest NOELs for reproductive toxicity were seen in the rabbit during organogenesis, where embryotoxic effects were seen at 0.33 mg/kg (NOEL 0.1 mg/kg).

No studies of reproductive toxicity in the target species were provided. As a consequence of this the CVMP has included a warning regarding the use of the product in pregnant animals in the SPC.

Mutagenicity

Gentamicin
A great number of *in vitro* or *in vivo* studies have been performed to define the mutagenic properties of gentamicin. While some positive results have been seen, in its MRL assessment for gentamicin, the CVMP concluded that the positive results were obtained in old and inadequate studies, and that they were not confirmed by more recent GLP-compliant experiments. Consequently, gentamicin is not considered to be a mutagenic compound (see published CVMP Summary Report for gentamicin for additional detail).

Miconazole
Data were provided from bacterial reverse mutation assays and an *in vivo* chromosome aberration study. Results of the bacterial mutation assays were negative. In the *in vivo* chromosome aberration study bone marrow cells and primary spermatocytes were examined following single and 5 daily intraperitoneal injections of miconazole with and without metabolic activation. Morphological abnormalities of the spermatocytes were seen as well as a dose-dependent increase in chromosome aberrations in both somatic and germinal cells. It was noted that the *in vivo* study was not GLP-compliant and that it lacked a positive control and consequently the results are questionable. Miconazole has been used in both veterinary and human medicine, and as transcutaneous absorption of the substance has been shown to be very low, miconazole present in Easotic does not represent a mutagenic concern for the target animal or for the pet owner.

Hydrocortisone acepoate (HCA)
A complete set of *in vitro* and *in vivo* tests for studying the genotoxicity of HCA was carried out (genetic mutation, chromosomal aberration and micronucleus test). All the studies were conducted according to GLP requirements and were in line with the appropriate guidelines. No evidence of mutagenicity was seen.

Carcinogenicity
No long term carcinogenicity studies were performed for gentamicin, miconazole or hydrocortisone aceponate. Given the lack of concern resulting from mutagenicity testing this is considered acceptable.

Studies of other effects

Miconazole and gentamicin
Neither miconazole nor gentamicin are known to possess immunotoxic potential and short- and long-term toxicity studies performed with the compounds did not reveal any adverse effects on the immune system.

Hydrocortisone aceponate (HCA)
In the subacute and chronic toxicity studies performed in laboratory animals HCA induced decreases in lymphocyte counts and increases in neutrophil and reticulocyte counts. Atrophy of the spleen and thymus were also observed. These effects are known effects associated with glucocorticoid therapy.

In the target species (dog) HCA in Dowanol solution at doses up to 11.4 mg HCA per animal for 14 consecutive days by the cutaneous route did not produce signs of immunotoxicity. No effect was observed on haematology parameters. In histological examination of lymph nodes, thymus and spleen the only effect seen was a decrease in axillary lymph node weight at the highest dose level (5 times the dose and twice the duration of treatment compared to the proposed product). Thus, even with large dosage, the risk of HCA-induced immunosuppression appears minimal. In a Buehler test performed in guinea pigs HCA in Dowanol solution did not produce was devoid of sensitising potential.

Easotic combination
To verify the lack of interactions between the three active principles present in Easotic, and to assess the potential risk for the user of the product, a Buehler test was performed in guinea pigs. This GLP-compliant test was conducted according to OECD guideline 406, and the results demonstrate a lack of sensitisation resulting from application of the suspension of HCA, miconazole and gentamicin.

Observations in humans
The three active substances of Easotic (gentamicin, miconazole and HCA) have been in used in Europe in human medicinal products for many years.

Microbiological studies (studies on human gut flora and organisms used in food processing)
Not relevant as Easotic is intended for use in dogs and not in food producing animals.

Studies on metabolites, impurities, other substances and formulation
No particular concerns relating to metabolites, impurities, other substances or the formulation have been identified.

User Safety

The intended therapeutic dose is 1 ml of the product in the ear, once daily. Since the treatment duration is 5 days, no chronic user exposure is expected with this product. The product is to be used by the veterinarian as well as by the pet owner and his/her family. The three active principles have been in use for many years in human medicine. They have a broad margin of safety, very low systemic absorption when applied on the skin and low acute and chronic toxicity profiles.

At low doses none of the active ingredients are reproductive toxins or teratogens. No carcinogenic data are available but the three well known active substances are not known to have any carcinogenic properties. In addition, cutaneous absorption is almost nil, lowering the risk of systemic effects, with the exception of glucocorticoid activity of HCA on the HPA axis. Data indicate that repeat use of the product will not cause sensitisation, and the risk of nephro- or ototoxicity associated with gentamicin is low following cutaneous and oral administration (potential exposure is low and cutaneous and oral bioavailability are almost nil).

The relevant potential exposure scenarios were considered and assessed the user safety associated with three scenarios in particular: skin exposure of non-professional users using the product (an acute exposure in which exposure to small amounts of the product may occur over 5 consecutive days), ocular exposure of non-professional users using the product following hand to eye contamination (an

acute exposure scenario with exposure to trace amounts over 5 consecutive days), and oral ingestion of the entire contents of the product by a child. The last scenario is considered to represent the greatest potential exposure.

With regards to dermal and ocular contact, it was considered that skin/eye irritation or skin sensitisation do not represent a concern as Easotic has been shown not to be irritant either to skin or eyes, and is not a skin sensitising agent.

With regards to the risk of accidental oral ingestion by a child, a quantitative risk characterisation was undertaken assuming a child weight of 15 kg and a maximum available volume of the product of 12 ml, which is considered to represent a worst case scenario. Margins of safety (MOS) were calculated using data from human medicine for each of the three active principles, as well as for the product using results from oral acute toxicity data obtained in rats. For these calculations, safety factors of 10 for intra and inter-species variability were always used. The margins of safety for each of the three active principles indicate that there is no risk of systemic toxicity following ingestion of the product by a child. Concerning the "potential risk" associated with the MOS for the product (MOS < 1), the applicant considers that the probability of a child ingesting the entire 10 ml contents of the vial is extremely low in practice. This is because the pump is clipped onto the bottle, and consequently it is not possible for a child to take the pump off the bottle.

The CVMP considers that a risk of transiently decreased blood cortisol levels in the case of a child ingesting the entire contents of the product is probable. However, the probability of ingesting the entire contents of the product is considered to be almost nil. Oral ingestion of less than 1 ml is considered to be more realistic. Thus, a maximal dose of 5 µg/kg HCA is to be suspected, and such an acute dose is not considered to represent a health concern.

The following risk management options are proposed for the product: Restriction of the distribution as a POM medicine: and restriction of application method as the product formulation and the dosing device have been developed to limit user's access to the product. Appropriate warnings have also been included in the SPC section 4.5. In conclusion, the user safety associated with the proposed product is considered to be acceptable.

Environmental Risk Assessment

The product is a veterinary medicinal product intended for an individual treatment in dogs only. The Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Products - Phase I (CVMP/VICH/592/98-FINAL) indicates that in case of drugs to be used for non-food animal species that there is no risk for the environment.

Conclusion on safety

The product is an auricular oily suspension containing three actives, namely HCA, miconazole and gentamicin. A complete set of safety studies was provided for HCA. Although both miconazole and gentamicin are compounds of "well-established use" according to Directive 2004/82/EC, a full bibliographic dossier has been provided, facilitating the risk analysis. The acute toxicity of HCA is well documented by a series of studies performed in various laboratory species. Hydrocortisone aceponate is of low toxicity regardless of the route of administration. Miconazole and gentamicin have higher intrinsic toxic potential but this countered by extremely low cutaneous bioavailabilities. Four recent GLP acute toxicity studies performed on the product have confirmed the low toxicity profile of Easotic and allow the product to be classified as not harmful.

The repeated dose toxicity of HCA is also well documented. A number of studies provided used the subcutaneous route of administration, which is appropriate for revealing the physiological and pathological changes associated with repeated exposure to the substance. The majority of the findings seen following subcutaneous administration are considerably reduced when administration is by the cutaneous route. The data are coherent with pharmacokinetic data. Observations made in repeated

dose toxicity and reproductive toxicity studies performed by the subcutaneous route are typical of high dose glucocorticoid activity.

After chronic oral dosing of miconazole to rats and dogs, the NOELs were found to be 3 and 10 mg/kg b.w., respectively. The only observed effect was induction of drug metabolising enzymes associated with increased liver weight.

The main well-known toxicological properties of gentamicin are nephro and oto-toxicity. However, these occur at high plasma concentrations, requiring intramuscular or intravenous administration. Pharmacokinetic data reveal that transcutaneous passage for miconazole and gentamicin is almost nil.

The applicant included a series of older studies examining the reproductive toxicity of miconazole and hydrocortisone aceponate. Miconazole had no impact on fertility, gestation period, perinatal and postnatal performance in rats and no teratogenic potential in rats and rabbits. Malformations observed at a high dose (100 mg/kg b.w) in both species were associated with maternal toxicity. Embryotoxic and teratogenic effect of hydrocortisone aceponate, including skeletal changes, reduction in foetal and placental weight and elevated post-implantation losses, were seen in rats and rabbits at higher doses (9 and 27 mg/kg b.w.). No effects were seen on the length of gestation in either species. A reduction in the survival of the resulting offspring was observed. The reproductive toxicity of gentamicin was documented bibliographically. No evidence of reproductive toxicity was observed in rats after administration by the intramuscular route at doses up to 15 mg/kg b.w. In three studies performed by the intramuscular route (rats) or subcutaneous route (mice), gentamicin was embryotoxic, but not teratogenic.

Hydrocortisone aceponate did not show any mutagenic potential in a series of recognised tests (genetic mutation, chromosomal aberration or micronucleus test). Furthermore, the metabolism and elimination of the substance is similar to that of the natural endogenous hydrocortisone compound. No long-term carcinogenicity studies have been performed. Gentamicin is not considered to have genotoxic potential. Similarly, miconazole does not belong to a chemical class known to have mutagenic potential. However, a published paper reports that miconazole produced a dose-dependant increase in chromosomal aberration in both somatic and germinal cells in mice. However, given the well established use of the substance, the fact that the published study lacked a positive control and that the transcutaneous absorption of miconazole is very low, the substance is not considered to represent a mutagenicity concern for the target animal or the user.

A comprehensive user safety assessment has been provided in line with the CVMP Guideline on User Safety for Pharmaceutical Veterinary Medicinal Products (EMEA/CVMP543/03-FINAL). The margins of safety calculated for the product are considered to be acceptable.

An environmental impact assessment performed in accordance with the CVMP Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I (CVMP/VICH/592/98-Final) has been provided, indicating that the product does not represent a risk to the environment.. A Phase I Environmental Impact Assessment is acceptable for this non-food animal product.

4. EFFICACY ASSESSMENT

PHARMACODYNAMICS

Besides some bibliographic data, the applicant provided the results of seven studies, of which 3 were GLP-compliant.

Gentamicin
Gentamicin is an aminoglycoside bactericidal antibiotic, which acts by inhibiting protein synthesis by binding to the bacterial 30S sub-unit of the ribosome. Its spectrum of activity includes Gram-positive and Gram-negative bacteria.

The Applicant provided three studies, one of them GLP-compliant, determining the *in-vitro* activity of gentamicin on bacterial strains isolated from clinical cases of canine otitis externa obtained during the clinical trials in France, Germany and Spain between 2004 and 2007. Samples were obtained from dogs with otitis externa prior to treatment and MIC values were determinated using Broth Microdilution Method and Trypcase Soya broth culture medium with an initial inoculum from a bacterial culture in the exponential growth phase. The bacteria strains most frequently isolated from canine otitis externa included *Staphylococcos spp, Streptococcus* spp., *Pseudomonas spp, Proteus spp.* and *Escherichia coli* and overall results show that the bacteria are reasonably susceptible against gentamicin. It was shown that (when administered as recommended), the concentration of gentamicin 14 days after first treatment still exceeded the MIC_{90} for the above pathogens.

Miconazole
Miconazole is a synthetic imidazole derivative with a pronounced antifungal activity. Miconazole selectively inhibits the synthesis of ergosterol, which is an essential component of the membrane of yeasts and fungi including *Malassezia pachydermatis*.

Two non-GLP studies were provided investigating the *in vitro* antifungal activity of miconazole nitrate and reference products against *Malassezia pachydermatis* from canine origin. Strains were isolated in the field clinical trial from otitis externa dogs in France, Germany or Spain during 2006-2007. Sensitivity was determined using calibrated inoculum of each strain mixed with the antifungal test substance. *Malassezia* colonies were counted (CFU) after up to 7 days incubation and compared to (untreated) control samples. Results demonstrated reasonable *in-vitro* activity of miconazole against several strains of *Malassezia pachydermatis*.

Hydrocortisone aceponate
Hydrocortisone belongs to the diesters class of the glucocorticosteroids with potent intrinsic glucocorticoid activity, resulting in a relief of inflammation and pruritus.

Two GLP-compliant studies were provided investigating the anti-inflammatory effect of topically applied hydrocortisone in a model of 12-0-tetradecanoylphorbol acetate (TPA)-induced ear oedema in mice following single topical administration. The results demonstrated a dose-dependent anti-inflammatory effect (reduction of oedema after 4 hours and 24 hours, respectively) of hydrocortisone aceponate applied topically before challenge in an inflammation model (TPA-induced oedema). At HPA concentrations of 1.25 µg/ml and higher a significant reduction in oedema was observed. No significant effects were detected on levels of inflammatory mediators PGE2, LTB4 and LXA4.

Dose determination

Justification of combination
Easotic is a fixed combination of three active substances (corticosteroid, antifungal and antibiotic). Clinical field trials confirmed otitis externa in dogs to be associated with Gram-positive bacteria (mainly *Staphylococcus* spp. and *Streptococcus* spp.), Gram negative bacteria (mainly *Pseudomonas* spp., *Proteus* spp. and *Escherichia coli*) and yeasts, principally *Malassezia pachydermatis*. The combination was justified to the CVMP with the broadening of the activity spectrum (inflammation,

microbial proliferation of fungi and/or bacteria) and easier animal handling, hence better owner compliance. The justification was considered acceptable by the CVMP.

Dose justification

The concentration of gentamicin and miconazole in the combination was justified by highlighting that daily administration of 2600 µg (i.e. 1505 IU) gentamicin and 15.1 mg miconazole would achieve concentrations in the ear canal higher than the MIC values for the main bacterial and fungal pathogens involved in otitis externa in dogs. This will allow the product to exert a bactericidal and fungicidal activity on ear pathogens. Studies showed long persistence of gentamicin (38 days) and miconazole (10 days) in the external ear canal of dogs at concentrations exceeding the MIC_{90} values. The concentration of HCA is based on pharmacodynamic data demonstrating an anti-inflammatory effect, i.e. reduction in oedema, in the ear canal at the proposed concentration.

Interaction between active substances and/or excipients

Two *in-vitro* studies investigating the potential interaction between gentamicin and miconazole against *Staphylococcus intermedius* and *Pseudomonas aeruginosa* and *Malassezia pachydermatis* were submitted. The bacteria were *in vitro* tested for their MIC_{90} values regarding the active substances alone and the mix of both substances. No indication of interaction was revealed and also, since each substance acts in different target cell types, no interaction would be anticipated. No specific studies were submitted for either hydrocortisone aceponate or paraffin in combination with the other ingredients. However, due to the different mode- and location of action, the likelihood of significant interaction appears small. Moreover, neither safety nor efficacy data gave rise to concerns regarding unfavourable interaction. Therefore, the CVMP concluded that no interaction would be anticipated.

Volume of single dose

The volume (1 ml) chosen for one dose may be considered too large a volume to be applied to very small dogs as the ear canal might be less than 0.8 ml. However, in the studies, 3.8% of dogs weighed less than 5 kg and 19.8% of dogs weighed from 5 to 10 kg and no particular problems were reported from veterinarians or animal owners involved in the studies. The CVMP accepted this explanation.

Dose determination studies

For dose determination, two well-designed GCP-compliant multicentre studies were conducted in the EU. In one study, three dosing regimes of Easotic were compared (once daily application for 7 and 14 days, and twice daily application for 7 days) in a total of 100 dogs. No statistically significant difference was demonstrated between groups and a single daily dose (for 7 days) was considered appropriate. In the second study including 120 dogs, a positive control group was included and the clinical as well as microbiological outcome was compared with two Easotic groups treated for 5 or 7 days. The clinical cure rates for Easotic treatments were in the range of 63-79% and no significant difference was observed between groups for either primary or secondary end points. Based on the data the CVMP agreed that a once daily application for 5 days would be an adequate dosing schedule.

Tolerance in the target species

Three target animal safety studies using Easotic in adult dogs and in puppies were provided. In general, the product was well tolerated in doses up to 5 X the RTD dose for twice the recommended treatment duration (up to 10 days). After 5 days of daily auricular applications, blood cortisol decrease (all doses) and some local, dose-dependent signs of irritation (erythema, redness) were observed in dogs treated 3 X and 5 X the RTD therapeutic dose; however, these signs of irritation where reversible and disappeared within 10 days after the last dosing. With increasing treatment duration, and in case of overdose, the observed effects (mainly local intolerance and strongly decreased blood cortisol levels) may be more marked, but remain reversible.

Resistance

Overall, the CVMP agreed that gentamicin and miconazole susceptibility for canine otitis isolates derived from the clinical trials from various locations in the EU was rather high. The Committee considered that sensitivity testing from ear isolates is of limited use since official breakpoints are based on plasma levels. Also, the presence of biofilm and exudate/cerumen may decrease efficacy and hence increase the risk of resistance development. Therefore, the concentrations of gentamicin and miconazole in Easotic are considerably higher than the MICs of resistant strains. Thus, at such concentrations even resistant strains in contact with the active substance are expected to be killed. In line with the current guideline on the SPC for antimicrobials (EMEA/CVMP/SAGAM/383441/2005) an appropriate warning was included in the SPC and package leaflet.

CLINICAL STUDIES

In support of the clinical efficacy of Easotic, two dose determination studies and one pivotal field study were submitted. In addition, some publications were provided regarding cytological evaluation and comparison of microbial isolates.

Field trials

The pivotal field study to support the clinical efficacy was a well-conducted GCP-compliant multicentric study conducted in 2006-2007 in a total of 32 centres in three EU countries. The trial assessed clinical and microbiological efficacy, as well as tolerance of Easotic in the recommended treatment dose (1 ml per ear/day over 5 days).

The study included a total of 176 dogs of various breeds and ages (5 months to 14 years), of which 152 were interpretable for the efficacy analysis and 173 for the safety analysis. The bodyweight ranged between 2.5 to 60 kg. Dogs suffering from acute or chronic cases of otitis externa were included in the trial (characterised by clinical signs of otitis externa and presence of bacteria and/or fungi at cytological examination). The micro-organisms isolated from the ears were considered representative in regards to spectrum and frequency. Treated animals were examined at the start and end of treatment (Day 0 and Day 5) up to 6 weeks after the end of treatment (i.e. days 7, 14 and 49)

Non-inclusion criteria were dogs with recent anti-fungal therapy, antibiotics, corticosteroids, cyclosporines within 15 days preceding the study (3 months for long-acting corticosteroids); negative cytology for bacterial and fungal populations or treated with a topical auricular antiseptic on day 0; pregnant or lactating bitches, animals with rupture of the tympanum, an associated pyoderma, parasitic otitis, otitis due to foreign body or advanced stages of proliferative or occlusive otitis. Exclusion criteria concerned animals that showed significant signs of intolerance to the product or that did not receive the whole treatment or were withdrawn by the owner from the trial. Also, dogs that received other (forbidden) treatments or that suffered from unilateral otitis at the visit of inclusion and from bilateral otitis during the follow-up were excluded.

Dogs were either treated with 1 ml Easotic per ear once a day for 5 days or with a positive control, authorised for the same indication in the EU and containing gentamicin, betamethasone and clotrimazole. Forbidden concomitant treatment consisted of anti-histamines, ear-cleaners, cyclosporine, systemic and auricular NSAIDs, corticosteroids, antibiotics and anti-fungal products.

Response variables were the reduction (%) of clinical score on day 14 (primary endpoint) and day 7 (both compared to day 0), the clinical cure on day 7 and on day 14, the cytological improvement on day 14 and clinical relapse. For the statistical analysis, the significance threshold was α=0.05.

The study showed a significant reduction in the clinical scores at day 14 (-83.2% ± 22.3) and day 7 (-80.9% ± 19.5), which were statistically similar to those of the control group (p=0.33 respectively p=0.99). A post-treatment effect was demonstrated by a larger reduction in the clinical score at day 14 as compared to day 7 (primary endpoint). The figures were reflected by clinical cure rates (defined by

the proportion of dogs with reduction rates exceeding 75%) of 64.6% and 72.2% for day 7 and 14, respectively, for Easotic, and 58.3% and 69.9% respectively, for the control group.

In the statistical analysis using the Wilcoxon test, of the reduction of the primary criterion "clinical score on Day 14", the estimated difference between Easotic and the positive control group was equal to 0 % and the lower bound of the confidence interval equal to - 6.7 %. The CVMP considered this analysis acceptable and concluded non-inferiority of Easotic in comparison to a positive control, which is a comparable product authorised for veterinary use in the EU.

The CVMP requested clarification on the inclusion of dogs with chronic otitis externa and the applicant clarified that "chronic cases" had at least one otitis episode in the year prior to the current otitis. Chronic cases included in the clinical study were dogs suffering from acute recurrence of chronic cases. By dividing the patients into an "acute otitis externa" group and an "recurrent otitis externa group", results for acute otitis externa showed a reduction in clinical score on day 14 of -85.8% ± 21.4% for Easotic as compared to -85.7 %± 19.9% for the control group. For dogs with recurrent otitis externa, the reduction in clinical score was -76.5 %± 23.7 % for Easotic as compared to -87.8% ± 13.0% for the control group. The relatively low clinical efficacy in the recurrent otitis externa group may be explained by the limited number of dogs included.

Clinical relapse was defined as an increase in the clinical score between day 14 and 28 at which the dogs required additional treatment despite being clinically cured on day 14. No cases of clinical relapse were recorded between day 14 and day 28. The CVMP expressed some concern to the short observation period since according to the CVMP Guideline for the demonstration of efficacy for veterinary medicinal products containing antimicrobial substances (EMEA/CVMP/627/01), post treatment follow-up should be performed for a sufficient time after the effects of treatment would be expected to have ceased. However, during the overall follow-up period (i.e. until Day 49), no dog clinically cured on Day 14 relapsed between Day 14 and Day 49 and the CVMP considered this satisfactory.

Bacteriological cure as a key parameter in assessing relapse was considered when bacteria isolated on day 0 were not any longer isolated at the post-treatment sample by day 49. Bacteriological cure was found satisfactory with 71.4% in the Easotic group and 75.7% in the control group. The applicant provided data on "Fungal cure rates" from the pivotal field trial as well as the dose confirmation study. While cure rates were not high they equal (or exceed) those for reference products.

Tolerance was assessed as the proportion of dogs with adverse events. Dogs belonging to the Easotic group (4.7%) and in the positive control (8.0%) indicated product-related adverse events during the follow-up with no statistically significant difference between groups (p=0.36). Most adverse events following Easotic administration were of dermatological origin, i.e. erythema. The clinical signs lasted a few days and all the dogs recovered, mostly without any specific treatment. Some dogs treated with Easotic showed clinical signs that were judged unlikely to be product-related including polyphagia, polydipsia, polyuria and incontinence, gingivitis, mild generalised pruritus, hot spot below treated ear+restlessness+nervousness and foreign body in ear canal. All dogs recovered within hours to 11 days. Two dogs received symptomatic treatment to control their adverse events.

Conclusion

The CVMP considered the clinical and bacteriological cure rates of Easotic as satisfactory evidence for the treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with bacteria susceptible to gentamicin and fungi susceptible to miconazole in particular *Malassezia pachydermatis*. The efficacy was statistically not different from the efficacy of an authorised veterinary product. Easotic was well tolerated with only mild dermatological reactions, which are transitory and reversible.

Compatibility with ear cleaners

In the field studies, use of ear cleaners was excluded since most ear cleaners have antimicrobial action, and their use could have interfered with the assessment of the efficacy of the tested product. The CVMP expressed some concern in relation to the use of ear cleaners or other biological materials that might impact on the efficacy of Easotic by acting as a mechanical barrier or to a lesser extent having a potential dilution effect. Since compatibility studies with ear cleaners have not been provided, an appropriate warning was included in the SPC.

Dogs with parasitic otitis were not included in the field study. However, the CVMP expressed some concerns with regard to dogs infected with *Demodex* spp. since Easotic may exert localised immunosuppression and induce an exacerbation of the disease. Although cases of generalised demodecosis extending to the ear are considered rare, the CVMP recommended to exclude dogs with demodecosis from treatment with Easotic and an appropriate warning is included in the SPC.

5. BENEFIT-RISK BALANCE

Benefit assessment

Easotic is a fixed combination ear drop suspension whose three active substances have the following actions: antibacterial, antifungal and anti-inflammatory. These combined actions are of value in the treatment of external ear infections in the dog. The antibacterial and anti-fungal components allow the bacterial and fungal components of the disease to be addressed whereas the anti-inflammatory component reduces the swelling of the ear and more importantly provides the dog with pain relief. Within a short time period the dog will have less inflammation including less pain, giving greater comfort to the animal. This means that there will be both less scratching of and less damage to the ear canal.

Easotic is manufactured using a standard manufacturing process and appropriate specifications have been set to ensure a product of consistent quality is produced. A shelf-life of 18 months and an in-use shelf-life of 10 days have been agreed based on stability data provided. A well conducted controlled clinical trial demonstrated that the product is efficacious in the treatment of acute otitis externa and acute exacerbations of recurrent otitis externa.

Risk assessment

The use of a miconazole and the potential for genotoxic effect was considered a concern. In the *in vivo* chromosome aberration study morphological abnormalities of the spermatocytes were seen as well as a dose-dependent increase in chromosome aberrations in both somatic and germinal cells. However, it was noted that the *in vivo* study was not GLP-compliant and that it lacked a positive control and consequently the results are questionable. The applicant has argued that miconazole has a well established use in both veterinary and human medicine, and that as transcutaneous absorption of the substance has been shown to be very low.

There is a lack of dose finding/dose confirmation studies in the dossier, however these studies are difficult to conduct for this type of product and a suitable justification was provided for the actives in the formulation.

A 5 day course of treatment as indicated in the pivotal field study, however, this may not be sufficient in all cases of otitis externa. CVMP recognised that veterinarians may need to continue treatment beyond 5 days. It was considered that such an extension is unlikely to compromise safety. The product is considered to be well tolerated and appropriate text has been included in the SPC and product literature to describe expected effects.

In terms of user safety, the risks associated with accidental dermal exposure or inadvertent oral contamination by adults and children are considered to be small. Warning statements for the person administering the product are included in the SPC section 4.5 Special precautions for use. A negligible risk to the environment was shown and the product is to be used for individual dogs.

The presence of a biofilm could interfere with the treatment. The SPC indicates in section 4.9 that the ear canal should be cleaned before application of the product.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit risk balance overall. The formulation and manufacture of Easotic is well described and specifications set will ensure that product of consistent quality will be produced. It is well tolerated by dogs and presents a low risk for users and the environment. Easotic has been shown to be efficacious for the indication 'Treatment of acute otitis externa, and acute exacerbation of recurrent otitis externa associated with bacteria susceptible to gentamicin and fungi susceptible to miconazole in particular *Malassezia pachydermatis*.'

Conclusion

The overall benefit risk analysis is deemed positive with a sufficiently clear and complete SPC and product literature. Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Easotic were considered to be in accordance with the requirements of Council Directive 2001/82/EC as amended.