SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

An application for the granting of a Community marketing authorisation for Posatex was submitted to the EMEA in October 2006 by S-P Veterinary in accordance with Council Regulation (EEC) No. 726/2004. Posatex contains orbifloxacin, mometasone furoate monohydrate and posaconazole and is presented in three different pack sizes containing 1 bottle each. It is indicated for the treatment of acute otitis externa and acute exacerbations of recurrent otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria.

The route of administration is auricular use. The target species is the dog and the product is administered once daily.

A detailed description of the pharmacovigilance system in place has been provided in the dossier. Upon review, the procedure and databases employed by Schering-Plough appear to be of good quality and are in line with the requirements of the legislation. The overall data provided are deemed satisfactory.

Satisfactory procedures with regard to manufacture, packaging, control and batch release arrangements are in place and the manufacturer is licensed to produce the finished product with the approved site of batch release located at S-P Bray, in Ireland.

2. QUALITY ASSESSMENT

Composition

Posatex Ear Drop suspension for dogs contains three active substances: orbifloxacin (8.549 mg/ml), mometasone furoate (as monohydrate) (0.855 mg/ ml) and posaconazole (0.855 mg/ ml) in suspension in a non-aqueous vehicle consisting of paraffin liquid and plasticised hydrocarbon gel (a mixture of 5% polyethylene in 95% mineral oil).

Container

Posatex is presented in 8.8 ml, 17.5 ml and 35.1 ml white opaque high density polyethylene (HDPE) plastic bottles with a white low density polyethylene (LDPE) cap, a natural or white LDPE applicator and a sheath.

Studies have been performed to establish the compatibility, safety and performance of the proposed container system. The finished product manufacturer's specifications for tip and sheath were provided at the request of the Committee. The specifications for the packaging components comprise tests for identity, physical characteristics. Compliance with EMEA/CVMP/205/04, Appendix II for non-solid dosage forms was shown. The component resins used in the bottle and cap have been tested and found to comply with the United States Pharmacopoeia (USP) requirements for Containers - Plastic (<661>). These resins have been and are currently being used in the packaging components of other veterinary ear drops which have been marketed in the EU for several years. Certificates of Analysis for the packaging components supplied by the finished product manufacturer (S-P, Bray, Ireland) were provided and deemed satisfactory.

Clinical Trial Formulae

The clinical batches were packaged in the same bottle, cap and mastitis tip which will be used for the commercial product. Drop weight data were presented for the 7.5 g bottle for three placebo formulation viscosities. The average drop weight corresponds with that given in the SPC.

Development Pharmaceutics

This product was developed as a suspension formulation because of the low solubility of the drug substances in both aqueous and oil media. Posaconazole is a broad-spectrum triazole antifungal agent and is expected to be 40-400 times more potent against yeast than clotrimazole. Mometasone furoate monohydrate is a synthetic steroid hormone in the glucocorticoid family. It is a potent anti-inflammatory agent and also shows antipruritic and vasoconstrictive actions. It is used topically in the treatment of corticoid-responsive dermatoses such as psoriasis and atopic dermatitis. Orbifloxacin is a potent, synthetic broad-spectrum antibacterial agent classified as a fluoroquinolone carboxylic acid derivative. Fluoroquinolones have the advantage over nonfluorinated quinolones of having significantly increased antibacterial activity at lower concentrations. Fluoroquinolones exhibit concentration-dependant bactericidal killing.

Formulation development focused on the physicochemical stability evaluation and product property characterisation. The Posatex suspension base is composed primarily of mineral oil (~97.3%). The solubility of orbifloxacin, mometasone furoate monohydrate and posaconazole in mineral oil was determined experimentally at room temperature. The particle size limits were justified for the micronised actives. The rheological properties were chosen to allow the product to have a high viscosity at rest and easy dispensing of the product once shaken. Stability studies demonstrated that the finished product is re-suspendable for all package presentations after vigourous shaking and that its resuspendability was well maintained over the shelf-life of the product.

Method of manufacture

The commercial batch size is 500 kg. A flow chart of the manufacturing process is provided along with a detailed description of the manufacturing process.

During manufacture, the active substances are dispersed in paraffin liquid and then plasticised hydrocarbon gel is added. The corresponding in-process controls are described (Active slurry preparation, Active slurry dispersion, Addition of Plastibase, Mixing/Homogenisation, Fill weight, Removal torque, Total process/hold time).

A validation protocol is provided. The process description and the in process controls are provided. Quality attributes tested in the validation are provided. Analytical results generated at the end of manufacturing and across the filling run within each validation batch will be evaluated for intra-batch and inter-batch variability.

Control of starting materials

Active substances

Orbifloxacin is purchased in the non-micronised form from Dainippon Pharmaceutical Company Ltd, Osaka, Japan and is micronised by Micron Technologies, Exton, PA, USA. A description of the micronisation process was provided along with the packaging used and certificates of analysis for both micronised and non-micronised forms. Orbifloxacin specifications (including loss on drying), manufacture description, development chemistry data and batch results are provided. Orbifloxacin has two crystal forms (form I and form II) and it exhibits a cis-3,5-dimethylpiperazine ring possessing two chiral centers. The cis-3,5-dimethyl-piperazine ring stereochemically belongs to a meso-form in which a plane of symmetry exists; therefore, Orbifloxacin is optically inactive, and no enantiomer can be isolated. However, there is a diastereomer owing to the dimethylpiperazine ring. Orbifloxacin is the cis form and the trans form is one of the potential impurities. Orbifloxacin impurities are discussed. A validated HPLC method for the determination of related compounds was provided. For orbifloxacin, a very stable compound, a re-test period of 4 years and no special storage conditions were retained based on data provided. The specification includes 0.2 % for individual impurities which is appropriate for an active substance used solely in veterinary medicine. The batch size was provided (89-97 kg) at the request of the Committee and certificates of analysis for the solvents and reagents

used. A limit for benzene will be routinely included in the toluene specification.

In the dossier submitted, Mometasone furoate monohydrate could be synthesised in two different ways: Process A (2 manufacturing sites: Schering Corporation, Union, New Jersey, USA and Schering Plough Products, Inc, Manati, Puerto Rico, USA) and Process B (batch size 30 kg -Schering-Plough Ltd, Singapore). However the applicant later withdrew Manati, Puerto Rico and Union, NJ as manufacturing sites for Mometasone furoate monohydrate. Additionally, the applicant withdrew Process A as this synthetic route is no longer used. Mometasone furoate monohydrate specifications, manufacture description, development chemistry data and batch results are provided. Certificates of analysis for the solvents and reagents used were provided to the Committee. A suitably validated HPLC method for the assay of mometasone and determination of related compounds was provided. Mometasone furoate can exist in two crystalline forms (pseudomorphs), the anhydrous form and the monohydrate form. At relatively higher temperature, 40° to 75°C and relatively long time periods, the monohydrate converted irreversibly to the anhydrous form. Mometasone furoate monohydrate potential isomerism is described. Mometasone furoate monohydrate impurities are discussed and suitable specifications set. For Mometasone furoate monohydrate, a retest period of 36 months when it is packaged in LDPE bags in fibreboard containers (*i.e.* protected from light) at refrigeration (2°C to 8°C) was accepted.

Posaconazole is manufactured at Schering-Plough, Rathdrum, Ireland with a typical batch size of about 180 kg. Posaconazole specifications, manufacture description, development chemistry data and batch results are provided. It was confirmed that process validation of the synthesis of posaconazole was conducted and the acceptance criteria were met. Certificates of analysis for the solvents and reagents, raw materials and intermediate products used were provided to the Committee. Posaconazole has been found to have three distinct polymorphs, designated as form I, form II and form IV. An additional meta-stable polymorph, form Ia forms and exists only at temperatures above 135°C. The presence of some amorphous posaconazole in the micronised drug substance was also observed. Posaconazole is a single stereoisomer containing 4 chiral centers and thus is optically active in solution. The manufacture of posaconazole is well controlled and a test for amorphous content in the specifications for posaconazole was included. X-ray diffraction analysis shows the drug substance to be highly crystalline. Optical rotation is performed at release in order to assure the correct stereochemistry. Posaconazole impurities are discussed and the total related compounds specification is set at NMT 0.80%. The retest period of 36 months proposed for posaconazole micronised drug substance when it is stored below 25°C in the commercial bulk drug substance container is acceptable.

Excipients

The excipients (Paraffin Liquid and Plastibase 50W) are described. It was confirmed to the Committee that mineral oil used will comply with the monograph for Paraffin Liquid, Ph.Eur.
Plastibase 50W is not described in a Pharmacopoeia but has already been accepted for the Otomax Ear drop suspension marketed in Europe. Certificates of analysis for the excipients were provided.

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

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies were addressed. A TSE/BSE statement from the finished product manufacturer is provided. The only substance derived from animal origin is Alphamethyl Epoxide used in the manufacture of Mometasone furoate monohydrate Process A. Process A is no longer to be used and therefore no certificate of suitability is required.

Control tests on the finished product

The finished product release specifications are provided. The total related compounds specification for each active was amended to NMT 1.5%. Particle size control, viscosity, and active substance polymorphic form were missing from the initial specifications provided. The specifications were revised to include particle size and viscosity control. A justification for the absence of active substance

polymorphic form in the final specifications was provided. The actives are suspended as solids in the non-aqueous matrix and a microscopic evaluation of the finished product will be conducted to confirm the crystal morphology. Some measure of resuspendability is also to be included in the finished product release and shelf-life specifications. The SPC includes a recommendation to shake the bottle before administering the product. The finished product control methods are described and validated. Batch analyses are provided.

Stability of the finished product

Finished product stability data are provided with shelf-life specifications. In view of the finished product release specifications and stability results, shelf-life assay specifications were revised as well as impurity specifications (individual and total). The proposed shelf-life specification for the assay of the actives is 93.0-107.0%. The upper limit is to be amended to 105%. Total impurities are set at ≤2.0% for Orbifloxacin ≤2.5% for mometasone furoate and ≤1.7% for posaconazole. The only trend observed for any chemical test conducted on batches of Posatex was for the degradation product of Mometasone furoate, compound E. As a result of the increase of Compound E at 25°C/60%RH over 36 months, the decision was made to refrigerate the product. Drug substance stability data show that the stereochemical purity of the actives is maintained under normal storage conditions and no testing on stability is required. A shelf-life of 24 months is agreed for Posatex stored in its primary packages under refrigerated conditions. The presence of extractable component coming from the label was observed during the finished product stability, a new label system that is free of benzophenone and Irgacure 184 has been selected for the commercial product. Demonstration that no extractable or leachable component coming from the new label used for the commercial product can be found in the finished product over its shelf-life is provided.

In-use stability tests

In-use stability data are provided for the 30g bottle supporting an in-use shelf-life of 28 days. All test results including assay, physical tests and microbial limits met the product specification and acceptance criteria. No data were provided for the other two smaller pack sizes. The applicant commits to conducting and providing additional in-use stability data simulating normal use after commercialisation as part of the on-going stability programme.

Overall conclusions on quality

Posatex ear drop suspension for dogs contains three active substances and is presented as a suspension containing liquid paraffin and plasticised hydrocarbon as the excipients. The product is presented in 8.8, 17.5 and 35.1 ml white HDPE bottles with a LDPE applicator. Dose accuracy has been demonstrated.

The product is manufactured using a standard manufacturing process involving dispersion of the active substances in the excipients. A process validation protocol has been provided. The manufacture of each of the active substances is described in detail in the dossier. The proposed specifications have been justified and impurities are controlled in line with VICH Topic GL10.

The product specifications include tests for the three active substances, description and identity, deliverable volume, assay and related compounds for each active and microbial limits. A test for viscosity and resuspendability and particle size control will be included at the request of the Committee. Analytical methods and validation for the veterinary medicinal product are generally considered acceptable. Batch data for several batches are provided in accordance with the specification.

Detailed specifications (including assay, related compounds microbial limits) for the product and routine tests for shelf-life are presented for the finished product. In view of the finished product stability results, shelf-life assay specifications will be reviewed. Impurity specifications (individual and total) were reviewed in detail and appropriate specifications set. Stability data under VICH

conditions has been presented in the packaging proposed for marketing. It has been accepted that changes in stereochemical purity are unlikely to occur on storage and microscopic evaluation of the finished product will be conducted to confirm the crystal morphology. A shelf-life of 2 years for the product stored in a refrigerator and also the product shall be stored in the original bottle and carton, was approved. An in-use shelf-life of 28 days was agreed.

3. SAFETY ASSESSMENT

Pharmacokinetics

The pharmacokinetics was investigated in healthy dogs in single dose studies performed under GLP conditions. Posatex formulations containing radiolabelled orbifloxacin, mometasone or posaconazole were applied topically in the ear of two dogs (1 male and 1 female). Radiolabelled posaconazole in the tested formulation was 10 times greater (1.0%) than in the intended formulation (0.1%) due to the low specific activity of the ^{14}C-posaconazole and in order to maximise the potential for detection of absorption. Orbifloxacin was well absorbed, but very slowly and the parent substance was excreted in faeces and urine. Following administration of radiolabelled mometasone and posaconazole radioactivity was also seen in faeces and urine, but not in the form of the parent compounds.

Data were also provided from studies in other laboratory species but these relate primarily to oral and parenteral administration.

The following text has been retained under SPC point 5.2 Pharmacokinetic particulars:

> *Systemic absorption of the active ingredients was determined in single-dose studies with [^{14}C]-orbifloxacin, [^{3}H]-mometasone furoate and [^{14}C]-posaconazole contained within the Posatex formulation and placed into the ear canals of normal Beagle dogs. Most of the absorption occurred in the first few days after administration. The extent of percutaneous absorption of topical medications is determined by many factors including the integrity of the epidermal barrier. Inflammation can increase the percutaneous absorption of veterinary medicinal products.*

Given the particular use of product in the dog, a more detailed summary of the absorption, distribution, metabolism, and excretion is not deemed necessary.

Toxicological studies

Single dose toxicity

Studies in rats and dogs indicate that the acute toxicity of orbifloxacin is low following oral administration.

The acute toxicity of mometasone furoate was low after oral administration to mice and rats and after subcutaneous administration to adult rats. Moderate toxicity was seen after subcutaneous administration to young mice and rats. Following administration by inhalation toxicity was low in rats, mice and dogs. The nature of the toxicity seen was as expected for a glucocorticoid drug.

Posaconazole was of low oral acute toxicity in mice and rats. Following intravenous administration toxicity was moderate and was affected by the vehicle used (less toxic in 5% aqueous dextrose than in hydroxypropyl-β-cyclodextrin). It is speculated that the degree of solubilisation may influence the bioavailability and consequently the toxicity. Signs of toxicity included pulmonary oedema.

Oral and dermal administration studies were also performed in rats with Orbimax otic suspension (10mg/g orbifloxacin, 1mg/g mometasone furoate and 1mg/g posaconazole) and toxicity was low in both cases.

Repeat dose toxicity

Several GLP compliant oral repeated dose toxicity studies were conducted with orbifloxacin in mice, rats and dogs. Effects were observed on the male reproductive system (rodents), kidney (nephritis in rats), liver (hepatocyte vacuolization in rats), gastro-intestinal tract (caecal enlargement in rats), spleen, cartilage (arthropathy in young dogs) and heart (QT prolongation in dogs). These findings are known adverse effects of quinolones/fluoroquinolones. NOELs of 80mg/kg, 20mg/kg and <3mg/kg were seen in mice, rats and young dogs (in which the NOEL was for arthropathy) respectively.

Data from GLP compliant repeated dose studies with mometasone furoate in mice, rats, dogs and rabbits have been provided. Regardless of the route of administration (oral, parenteral, dermal, intranasal), adverse effects observed were typical corticoid effects (reduction of food consumption and body weight; reduction of spleen, adrenal and thymus weight; and at higher dosages, lymphoid atrophy in spleen, thymus, adrenal gland and lymphoid organs). Progestogenic effects were reported in rats after oral administration (this effect disappeared after a 4-week recovery period) and dermal application to rabbits. No progestogenic effects were reported in mice and dogs. No clear NOEL could be retained for oral administration - the lowest oral dose tested was 1.25 µg/kg (3-month toxicity study in rats with decreased body weights in females). No dermal NOEL could be retained for rabbits - the lowest dermal dose tested was 50 µg/kg. After intranasal administration of a suspension of mometasone to dogs, the NOEL was 15 µg/kg.

GLP compliant oral administration studies with posaconazole were performed in mice, rats, dogs and monkeys. The main findings were consistent with phospholipidosis. Effects were also seen in reproductive organs and adrenal glands and are considered to be a result of posaconazole's effects on steroidogenesis and so to correlate with the substance's mechanism of action. The lowest NOEL was 1 mg/kg bw/day.

Reproductive toxicity

Two GLP compliant reproductive toxicity studies were conducted in rats with orally administered orbifloxacin. No effects on male or female fertility were seen. Effects on prenatal and/or neonatal parameters were observed at maternotoxic doses (the lowest NOEL for was 50 mg/kg). Four GLP compliant embryo/foetotoxicity developmental studies were conducted with orbifloxacin (2 in rats and 2 in rabbits). No evidence of teratogenicity was seen. Embryo/foetotoxicity was noted in both rats and rabbits at maternotoxic doses (the lowest NOEL for embryo/foetotoxicity was 50 mg/kg in rats). Maternotoxic effects reported in rabbits at doses above 200 mg/kg were typical for quinolones (non systemic disturbances on the intestinal flora of rabbits).

Two GLP compliant reproductive toxicity studies were conducted in rats with subcutaneously administered mometasone furoate. No effects on fertility were noted. The main adverse effect was a difficult and prolonged labour. The lowest NOEL was 2.5 µg/kg. Five GLP compliant embryo/foetotoxicity studies were conducted in mice (subcutaneous), rats (subcutaneous, dermal) and rabbits (oral, dermal). Teratogenic effects were seen in rabbits following oral administration (cleft palate, hydrocephaly) of mometasone furoate at maternotoxic doses. The NOEL for this effect was 140 µg/kg. These effects are consistent with the known teratogenic effects of corticosteroids in laboratory species. Similar effects are not expected in humans. No teratogenic effects were seen in mice or rats. Embryotoxic/foetotoxic effects were reported at maternotoxic doses in rabbits and rats, with NOELs of 140 µg/kg in rabbits (subcutaneous administration) and 2.5 µg/kg in rats (subcutaneous administration), respectively. No NOEL was established following dermal application in rabbits (< 150 µg/kg).

Three GLP compliant fertility studies were conducted in rats with posaconazole. No major effects on fertility were seen after oral administration. However, in one study (ref. 234), at 45 mg/kg a significant increase in the number of resorptions was observed. The lowest NOEL for toxicity to fertility was 30 mg/kg. Five GLP compliant embryo/foetotoxicity developmental studies were conducted with posaconazole in rats and rabbits. No evidence of teratogenicity was reported. Embryo/foetotoxicity was noted in both rats and rabbits at maternotoxic doses. The lowest NOEL for embryo/foetotoxicity was 6 mg/kg (from a peri-and post-natal developmental study in rats)

The product is contraindicated in breeding and pregnant dogs.

Mutagenicity

Orbifloxacin was tested in bacterial mutagenicity studies, cultured L5178Y mouse lymphoma cells (mouse lymphoma TK assay), cultured human peripheral blood lymphocytes, an *in vivo-in vitro*

unscheduled DNA synthesis study and an *in vivo* mouse bone marrow micronucleus test. In the bacterial mutagenicity tests positive results were seen in *Salmonella typhimurium* strain TA102. This result is consistent with the known effects of fluoroquinolones, which interact with bacterial topoisomerase II. Since mammalian topoisomerase II is known to be less sensitive to fluoroquinolones than the bacterial enzyme, the positive result in TA 102 is considered to have little relevance to humans and dogs.

Positive results were also seen in *in vitro* mouse lymphoma TK cells (gene mutation) and in cultured human peripheral lymphocytes (chromosome aberrations) but only at high concentrations. These results are in line with the known positive *in vitro* effects of fluoroquinolones, while the two *in vivo* assays both gave clear negative results. Overall orbifloxacin should not be considered to be mutagenic in humans or dogs.

Mometasone furoate was tested in bacterial mutagenicity studies, cultured L5178Y mouse lymphoma cells (mouse lymphoma TK assay), cultured Chinese hamster ovary cells (chromosome aberration test), an *in vivo-in vitro* unscheduled DNA synthesis study, an *in vivo* mouse bone marrow micronucleus test and in an *in vivo* chromosome aberration test in spermatagonial cells of mice. No evidence of genotoxicity was seen except in the *in vitro* chromosome aberration assay in cultured CHO cells where positive results were seen but only at cytotoxic concentrations and without metabolic activation. The result is consistent with those of other corticosteroids and is considered to be a class effect and not to represent direct interaction with DNA. Overall, mometasone furoate was not considered to be mutagenic.

Posaconazole was tested in bacterial mutagenicity studies, cultured Chinese hamster ovary cells, cultured human peripheral lymphocytes and in an *in vivo* mouse bone marrow micronucleus test. No evidence of genotoxicity was seen except for in cultured human peripheral lymphocytes, where an increased number of polyploidy cells were seen. The effect was slight and occurred at only one harvest interval. As the *in vivo* assay showed no evidence of genotoxicity it was considered that overall, posaconazole is not mutagenic.

Carcinogenicity

Since orbifloxacin is not considered to be genotoxic carcinogenicity tests are not required. However, orbifloxacin has been tested in carcinogenicity studies both mice and rats and was not found to be carcinogenic at daily oral doses of 200 mg/kg for 2 years (the maximum dose tested in both species)

Since mometasone furoate is not considered to be genotoxic carcinogenicity tests are not required. However, carcinogenicity studies have been performed with mometasone furoate in mice and rats, using nose-only inhalation both species. No carcinogenic effects considered to be of significance for dogs or humans, were seen.

Since posaconazole is not considered to be genotoxic carcinogenicity tests are not required. However, posaconazole has been tested in carcinogenicity studies in both mice and rats. At high oral doses an increased incidence of adrenal tumours was noted but this is not considered to be of significance for the proposed auricular administration product.

Studies of other effects

Ocular and dermal irritation studies have been performed with orbifloxacin and mometasone furoate. Orbifloxacin was not irritating to rabbits' eyes or to intact rabbit skin. Nor did it produce dermal sensitisation in guinea pigs. Mometasone furoate (formulated as a cream) was slightly irritating to rabbits' eyes and dermal effects were typical of corticosteroids. Mometasone furoate was not considered to be a dermal sensitiser in guinea pigs.

Posaconazole is not considered to be a dermal sensitiser in guinea pigs. Posaconazole was also tested for effects on calcium homeostasis in rats, immunotoxicity in mice and coagulopathy in dogs. No effects considered to be significant for the proposed product were reported.

The effects of orbifloxacin on articular cartilage of young dogs were also investigated. Oral administration of the substance produced effects consistent with arthropathy with a NOEL of 2 mg/kg. The effect is a known effect of fluoroquinolones.

Studies of ocular and dermal irritation as well as dermal sensitisation have also been undertaken with the final formulation. Eye irritation results showed slight redness one hour after instillation while no evidence of dermal irritation was seen in intact skin and no evidence of dermal sensitisation was seen. Dermal irritation is discussed further under the heading of Tolerance in the target species in section 4.

Observations in humans

Orbifloxacin is not used in humans and consequently no data were presented. Mometasone furoate and posaconazole are used in inhalers in the treatment of asthma and in an oral suspension for the treatment of invasive fungal infections, respectively. Minimal data were provided from experience gained with human use. A NOEL of 400mg/day was established for single oral administration of posaconazole in humans.

User safety

In the user safety assessment, the different scenarios, which are in line with the use of the veterinary medicinal product, Posatex, were presented. In general, the margins of safety obtained were sufficiently high, with few values less than 100, which takes into account the interindividual and interspecies variability. Considering that the type and level of exposure are of low probability, the margins of safety obtained are considered acceptable. The statements proposed in the SPC reinforce the conclusion that Posatex will not constitute an unacceptable acute or chronic risk following accidental dermal exposure or inadvertent oral contamination by adults and children.

Environmental risk assessment

A phase I environmental risk assessment in accordance with VICH GL 6 has been conducted by the applicant. Since Posatex is for use in dogs, no phase II assessment is required. Overall, it is considered that when used as recommended the environmental impact of Posatex will be negligible.

Overall conclusions on the safety documentation

The impact of Posatex, in terms of safety for animals, user safety and environmental toxicity, when used as recommended can be considered as negligible.

4. EFFICACY ASSESSMENT

Pharmacodynamics

Posatex contains three active substances: orbifloxacin, posaconazole, and mometasone. Orbifloxacin is a bactericidal fluoroquinolone antibiotic which interferes with the enzymes DNA topoisomerase II (DNA gyrase) and DNA topoisomerase IV. Posaconazole is primarily an antifungal agent, although it also has weak antibacterial activity. It selectively inhibits the enzyme CYP51 involved in ergosterol biosynthesis in yeasts and filamentous fungi. Mometasone is a potent glucocorticosteroid and has anti-inflammatory action.

A pharmacological study was performed to assess the *in vitro* potentiation or inhibition of efficacy of the combination of the three active substances. The combination exhibited neither synergism nor antagonism against isolated strains of *Staphylococcus intermedius, Pseudomonas aeruginosa* and *Malassezia pachydermatis.*

For orbifloxacin, a study conducted in Europe was not conclusive for MIC, because of the low number of strains isolated. Additional data from the EU field study on sensitivity to orbifloxacin relating to appropriate bacterial strains was provided at the request of the Committee. For posaconazole, the applicant discussed the difficulty of standardising MIC determinations which lead to differences between results of both studies conducted in France and UK for MIC.

Development of resistance

The usefulness of MIC data for a local treatment is debatable. However, it gives some measure of the bacterial population to be treated. Orbifloxacin is a concentration-dependent bactericidal antibiotic which will be applied to the ear canal at ~ 1000 x MIC of the pathogens being treated. It is not expected that there will be increased emergence of fluoroquinolone resistance with the topical use as indicated for Posatex.

Malassezia pachydermatis has not shown any resistance to antifungal agents commonly used against yeasts. Ototopical use of posaconazole is directed at controlling *Malassezia* and a supraoptimal concentration of posaconazole is applied directly to the site of infection. The concentration of posaconazole within Posatex is 850X the MIC_{90} and resistance is unlikely to be induced.

The types and mechanisms of acquired resistance were discussed and also the occurrence of cross-resistance and co-resistance. Cross resistance across the fluoroquinolone class of antibiotics is common and this is included in the SPC.

Target Animal Tolerance

Studies with the final formulation of Posatex in rats showed that acute toxicity of Posatex (final formulation) was low in rats after oral administration and dermal application in intact skin. Possible effects after dermal application on abraded skin were discussed. Mometasone was evaluated for dermal irritation and systemic toxicity in white rabbits and the conclusions were that topical application in rabbits with intact or abraded skin produced local and systemic changes typical of corticosteroids. With all corticosteroids there is the potential for delayed wound healing, however, when the product is used as directed no delayed wound healing is expected.

Two tolerance studies were conducted on Beagle dogs. In the first GLP study, the dogs received the veterinary medicinal product at up to 5 times the recommended dosage for 21 days (both ears were treated). A recovery period (13 days) followed for control (vehicle only) and 1 time treated groups. Red discolouration of the skin of the ears was observed several times in dogs in all groups, including the control, and persisted more than 13 days. The severity of erythema was scored and was quite mild and sporadic. This effect is probably due to the vehicle and has been specified in the SPC as an adverse effect (section 4.6. Adverse reactions). In ACTH-stimulation tests, post-stimulation cortisol

levels were slightly decreased in the 5x group compared to the control group on Day 21; this is documented in the SPC (section 4.10. Overdose).

Laboratory studies in puppies using orbifloxacin have shown evidence of arthropathy after systemic administration. A warning statement is included on the SPC (section 4.5. Special precautions for use).

The safety was not assessed in pregnant or lactating bitches. Due to embryotoxic and/or teratogenic properties of the active substances noted in laboratory species, a suitable warning concerning use during pregnancy and lactation has been included in the SPC section 4.7. Use during pregnancy and lactation.

In the second non-GLP study, the veterinary medicinal product was instilled in both ears of 4 dogs at the recommended daily dose, instilled for 14 days (the proposed maximum recommended duration was 21 days). Red bumps, which resolved within 2 days, were noted on the pinnae on Days 8 and 11 after the beginning of treatment.

Below 7 months no safety data were available. Analytical evaluation of tolerance was conducted; use in animals less than 4 months of age is not recommended (SPC section 4.5) as quinolones have been associated with cartilage erosions in weight bearing joints and other forms of arthropathy.

As a whole, the product is well tolerated if used according to recommendations in the SPC.

In the target species tolerance study, the smallest dog used weighed 6.17 kg and the exposure for a light body weight dog over 7 days would be greater than for a heavier weight dog. The pivotal study demonstrated that when Posatex is given at 3x the recommended dose for 21 days, the cumulative exposure was exceeded for a 1.5 kg dog however no HPA suppression was reported. The dose was restricted to only 2 drops per ear for toy dog breeds to increase the margin of safety. Two clinical trials enrolled various small breed dogs without adverse events. The SPC section 4.9 details the number of drops to be applied based on a weight range (under 2 kg to 15 kg or more) for the dog.

Dose determination / confirmation

No dose finding or dose confirmation studies were submitted and, therefore, it is difficult to conclude if the proposed dosage regimen is optimal in terms of achieving efficacy without relapse and minimising the potential of the product to select for antimicrobial resistance. A justification was provided for the concentration of the actives in the formulation and the CVMP accepted that the dosage regimen would ensure therapeutic efficacy and limit the selection of antimicrobial resistant bacteria. The once daily dosing for a treatment period of 7 days was shown to be efficacious. The applicant provided a PK-PD analysis which argues that the concentrations of the antimicrobials at the surface of the ear canal will be many times higher than the MICs of susceptible organisms, and that otitis externa is typically a superficial infection.

In the pivotal clinical study, 53.5 % of cases were categorised as either recurrent or chronic. Although *Malassezia* organisms do not invade subcorneally, bacteria such as *S. intermedius* may invade more deeply into the epidermal layers and appendages in these types of infections. In these cases, infection is no longer superficial and the rate of release of active substances from the vehicle, penetration and rate of absorption through the skin is relevant.

Field trials

Two field studies were submitted. No experimental study was presented in the target species. Clinical studies were well conducted under GCP conditions.

In the field study, conducted in veterinary clinics in the USA in 2000, a negative control was used to assess the field efficacy and safety of Orbimax otic and Mometamax otic suspension administered once daily.

This was a multi-centred, comparative, blinded, randomised study, conducted in accordance with GCP procedures. Dogs of various breeds, ages, sex and weight, were presented for diagnosis and treatment of **combined** bacterial and yeast otitis. A wide cross-section of the canine population (49 breeds and mixed breeds) was represented. Both sexes were equally represented. The presence or absence of ear mites was noted on the cytology form. Owner consent was obtained prior to the animal being enrolled in the study.

Dogs with otic foreign bodies, dogs with a ruptured tympanic membrane, dogs with neoplastic or non neoplastic masses that occlude the ear canal, dogs owned by clinic veterinarians or staff were all excluded from the study. Also any dogs treated, at the time of enrolment, with:

- any otic corticosteroid, antibiotic and/or antifungal therapy within the previous 5 days,
- any short or intermediate acting systemic corticosteroid within the previous 5 days,
- any long-acting systemic corticosteroid within the previous 4 weeks,
- any systemic antimicrobial and/or antifungal therapy within the previous 7 days, were excluded.

On day 0, after physical and bacteriological examinations (specimen collection), ears were cleaned with a physiologic saline or water solution. After day 0, the only acceptable cleaning procedure was the use of a cotton ball (or equivalent) to gently remove excess exudates, if necessary. Rigorous cleaning or irrigation of ear canals was not permitted after day 0.
Either the control Mometamax (a combination of gentamicin sulphate, clotrimazole and mometasone furoate) or the test product Orbimax Otic (same as Posatex) or control Vehicle (mineral oil) was applied once daily for 7 consecutive days (day 0 to day 6). Dogs under 15 kg received 4 drops per affected ear; dogs over 15 kg received 8 drops. After treatment, the ears were massaged.

Clinical examinations were conducted at day 0 and 2 to 7 days following termination of treatment.

Cytology procedure: a qualified ear was clinically and cytologically tested (one per dog. Right ear *a priori,* and left ear if right ear can not be enrolled after cytology examination)

- Prior to initial treatment, clinicians took a sterile swab specimen for preparation of a roll smear on a glass slide, then stained using Diff-Quick or equivalent stains and microscopically examined. Confirmation of both yeast (*Malassezia spp.*) and bacteria for enrolling the animal in study.
- Cytology was repeated at the time of study termination.

Bacteriological (day 0 and 2 to 7 days following termination treatment): swabs from qualified ear were taken for culture. All organisms were identified by genus and species. Orbifloxacin and gentamicin MICs were determined for all isolated bacteria, in each group, before and after treatment.

Overall evaluation by the clinician (excellent/good/fair/poor: based on clinical criteria) and by the owner was noted at the time of the last visit. Analysis: ANOVA for age and weight.

For the three pivotal variables (discomfort, ear canal erythema and ear canal swelling), within group analysis from day 0 to study completion were performed over the treatment period. Analysis was by marginal homogeneity exact test (Chi Square Test). Statistical significance was declared at $p < 0.05$. Preliminary significance was declared when $0.05<p<0.10$.

Results

From the dogs included (60 % assigned to Orbimax group, 20 % to Mometamax group and 20 % to negative control group), **83 % of cases** were analysed: 51 % of cases for Orbimax group, 16 % for Mometamax group and 16 % for the negative control group. 17 % of cases were unqualified: most of them for protocol violations or because of insufficient wash-out period before re-evaluation. All dogs were included for assessment of safety.

On day 0, there was no difference between treatment groups, except for age (dogs in Orbimax and Mometamax groups were older than control negative ones: respectively 6.1 years, 6.6 years *versus* 4.9 years). In three groups, otitis were clinically and bacteriologically similar: cases were distributed between acute, recurrent and chronic externa otitis. Otitis was mainly bilateral.

Evaluation cases per group	**Acute otitis**	**Recurrent otitis**	**Chronic otitis**
Orbimax (Posatex)	48 (39.3%)	55 (45.1%)	19 (15.6%)
Mometamax	12 (31.6%)	20 (52.6%)	6 (15.8%)
Negative control	14 (36.8%)	19 (50.0%)	5 (13.2%)

Discomfort, inflammation, swelling and odour were present in most cases (between 85-100% of cases in each group) on day 0, without significant differences between the three groups.

On day 0, in the Orbimax group, the most common bacteria isolated was *Bacillus spp.* (30 cases), *Enterococcus spp.* (23 cases), *Staphylococcus* coagulase positive (23 cases) and *Pseudomonas aeruginosa* (14 cases).
On day 0, in the Mometamax group, the most common bacteria isolated was *Staphylococcus* coagulase positive (15 cases), *Bacillus spp.* (9 cases) and *Corynebacterium spp.* (6 cases).
On day 0, in negative control group, the most common bacteria isolated were *Bacillus spp.* (12 cases), *Staphylococcus* coagulase positive (11 cases) and *Staphylococcus* coagulase negative (5 cases).

On day 8, in the Orbimax group, the most common bacteria isolated was *Corynebacterium spp.* (22 cases), *Staphylococcus* coagulase positive (12 cases), *Pseudomonas aeruginosa* (7 cases), *Staphylococcus* coagulase negative (7 cases), *Enterococcus spp.* (7 cases) and *Bacillus spp.* (5 cases).
On day 8, in the Mometamax group, the most common bacteria isolated were *Staphylococcus* coagulase positive (8 cases).
On day 8, in negative control group, the most common bacteria isolated was *Staphylococcus* coagulase positive (9 cases), *Bacillus spp.* (8 cases) and *Pseudomonas* not *aeruginosa* (4 cases).

A reduction of bacteria in culture after treatment was observed in each Orbimax and Mometamax group but not in the negative control group. However, a bacterial cure was not confirmed in these groups. No significant differences of orbifloxacin and gentamicin MICs, before and after treatment, were observed. After termination of treatment (noted as day 8 in this study), a reduction of presence of *Malassezia spp.* on cytology, and many of the buds were not viable after treatment with Orbimax or Mometamax (results of *Malassezia* culture indicated a poor growth of yeast, only 10% of positive culture in Orbimax group at day 8, versus nearly 70% at day 0).

For the Orbimax group, Mometamax group and vehicle group, the percentage of cases that exhibited improvement at day 8 was respectively :
- for discomfort : 88.1%, 74.3% and 44.7%.
- for ear canal erythema : 81.1%, 73.7% and 39.5%
- for ear canal swelling : 83,2%, 70,6% and 48.6%.

For otitis, the number of cases resolved with Orbimax and Mometamax were proportionally similar, and there was no statistical difference between these two groups for resolution of clinical parameters, and no difference on the investigator's and owner's overall evaluation. There was a statistical difference between each of these two groups and vehicle group for resolution of clinical parameters and on the investigator's and owners overall evaluation.

One adverse reaction was reported in a case of bilateral otitis. The investigator observed a hearing loss on day 4 in an Orbimax-treated dog. The condition resolved after 1 week.

Discussion
Posatex produced a good improvement in clinical parameters when compared to the negative control (vehicle) group. In this study, a group received only placebo (vehicle), confirming statistically significant improvement in clinical signs when treating with Posatex versus placebo. But this study did not by itself confirm the justification of the combination contained in Posatex but is supportive in nature. It is accepted that this type of combination has its place in the treatment of bacterial dermatitis with fungal overgrowth. With a high level of inflammation, the use of mometasone is justified.

Mometamax (mometasone furoate, clotrimazole and gentamicin sulphate) is not registered in Europe and is licensed for once daily use in the US.

A statistical analysis was performed on all cases, however, in veterinary practice, dogs may be treated according to clinical symptoms and results of a roll smear, without a laboratory confirmation. Ear mites were not in the exclusion criteria; only one case was registered in the control negative group.

Chronic otitis was observed in a few cases (15.2 % of the dogs in the efficacy evaluation, with only 6 cases in Mometamax group and 5 cases in negative control group). In the SPC section 4.2 the indication specifies 'treatment of acute otitis externa and acute exacerbations of recurrent otitis externa.'

Cytology procedure:
- presence of bacteria was not characterised by invasion or colonisation; presence or absence of pyonuclear cell (intracellular bacteria in neutrophilia polynuclear cells) was not reported. The existence of commensal flora (non pathologic bacteria) in some cytologic samples is to be expected.

The second field study was a positively controlled study to assess the field efficacy and safety of Orbimax Otic Suspension administered once daily in the treatment of otitis externa in comparison with a reference product, Surolan (polymyxin B sulfate, miconazole nitrate, prednisolone acetate, mineral oil vehicle system) (Janssen-Cilag).

This was a multi-centred, comparative, blinded, randomised study, conducted in accordance with GCP procedures in 15 veterinary clinics in France, Belgium and Germany, from November 2000 to May 2001. Dogs of various breeds, ages, sex and weight were enrolled and presented for diagnosis and treatment of combined bacterial and yeast otitis. A wide cross-section of the canine population (52 breeds and mixed breeds) was represented. Males and females were equally represented. The presence or absence of ear mite was noted on the cytology form. Owner consent was obtained prior to the animal being enrolled in the study.

Dogs with otic foreign bodies, dogs with a ruptured tympanic membrane, dogs with neoplastic or non neoplastic masses that occlude the ear canal, dogs owned by clinic veterinarians or staff were excluded from the study. Dogs treated, at the time of enrolment, with :
- any otic corticosteroid, antibiotic and/or antifungal therapy within the previous 5 days,
- any short or intermediate acting systemic corticosteroid within the previous 5 days,
- any long-acting systemic corticosteroid within the previous 4 weeks,
- any systemic antimicrobial and/ or antifungal therapy within the previous 7 days were also excluded.

On day 0, after physical and bacteriological examinations (specimen collection), ears were cleaned with a physiologic saline or water solution. After day 0, the only acceptable cleaning procedure was the use of a cotton ball (or equivalent) to gently remove excess exudates, if necessary. Rigorous cleaning or irrigation of ear canals was not permitted after day 0. Orbimax Otic was applied once daily for 7 consecutive days (day 0 to day 6). Dogs under 15 kg received 4 drops per affected ear, dogs over 15 kg received 8 drops. After treatment, ears were massaged. Surolan was applied twice daily for 7 consecutive days (day 0 to day 6). Dogs received 4 drops per affected ear.

The primary pivotal variable was treatment success or failure.

Clinical examination (visit 1, noted V1, at day 0 and visit 2, noted V2, at day 8 to 10, 2 to 4 days following termination treatment)
- Pivotal clinical variables :

- Discomfort (0 : none, 1 : mild, 2 : moderate, or 3 : marked),
- External ear canal exsudate quantity (0 : none, 1 : residual – trace amount, 2 : mild to moderate – visible on the lining of ear canal, 3 : marked – fills canal and obstructs otoscopic examination),
- external ear canal erythema (0 : none - normal, 1 : mild – slight pink, 2 : moderate - pink, or 3 : marked - red),

- external ear canal swelling (0 : none - normal, 1 : mild, 2 : moderate, or 3 : marked).

- Non-pivotal clinical variables :
- external ear canal exudates type (1 : serous, 2 : waxy, or 3 : purulent),
- odour (0 : no, 1 : yes)
- pinna erythema (0 : none - normal, 1 : mild – slight pink, 2 : moderate - pink, or 3 : marked - red),
- a hearing (clap) test was performed to assess hearing in both ears.

Investigator overall evaluation and owner overall evaluation were non-pivotal variables. Evaluation criteria (at the post-treatment evaluation) were: excellent, good, fair or poor.

Cytology procedure:
- Prior to initial treatment, clinicians took a sterile swab specimen for preparation of a roll smear on a glass slide, then stained using Diff-Quick or equivalent stains and microscopically examined. Confirmation of both yeast (*Malassezia spp.*) and bacteria for enrolling the animal in study.
- Cytology was repeated at the time of study termination.

Bacteriological (V1 and V2): swabs from qualified ear were taken for culture. All organisms were identified by genera and species. Orbifloxacin and polymyxin B MICs were determined for all isolated bacteria.

Overall evaluation by the clinician (excellent/good/fair/poor: based on clinical criteria) and by the owner was noted at the time of the last visit.

The equivalence between products (Orbimax otic and Surolan) was demonstrated by confirming that the difference between the success proportions was within an interval of 80-120%, with a 90% confidence interval. Preliminary statistical significance and statistical significance were respectively declared when $0.05<P<0.10$, and $p<0.05$.

Results

No statistically significant differences in baseline characteristics were noted between the 2 treatment groups, except for the number of neutered dogs and the number of dogs with previous dermatological disorders (fewer in Orbimax group).

From the dogs included (49 % assigned to Orbimax group and 51 % to Surolan group), 78 % were kept for efficacy analysis, after excluding cases not compliant with protocol: 35 % for Orbimax group and 43 % for Surolan group.

The mean and median age for enrolled cases in the Orbimax group was respectively 5.0 and 4.5 years. The mean and median age for enrolled cases in Surolan group was, respectively, 5.5 and 4.6 years. Enrolled dogs ranged in age from 0.3 to 14.3 years and in weight from 3.2 to 68.0 kg.

In the two groups, otitis was clinically and bacteriologically similar: cases were distributed between acute, recurrent and chronic externa otitis. Otitis was mainly bilateral.

Evaluation cases	**Acute otitis**	**Recurrent otitis**	**Chronic otitis**
Orbimax group	(49.0%)	(36.0%)	(15.0%)
Surolan group	(44.1%)	(41.2%)	(14.7%)

At visit Number 1, the pivotal clinical variables (discomfort, external ear canal exudate quantity, external ear canal erythema, and external ear canal swelling) were not significantly different between the two groups.

At visit Number 2, all 4 pivotal clinical variables scores markedly improved during the study in both treatment groups. Statistically significant improvement (p<0,0001) was confirmed in Orbimax group (not evaluated in the Surolan group). Only the pivotal clinical variable of discomfort was significantly better in Orbimax group than in Surolan group. All other clinical variables improved without significantly differences. The two populations studied (Intent-to-treat and per protocol) gave similar results. The success rates (based on primary pivotal criteria) ranged from 94% to 95% in both groups. The secondary variables (odour, pinna erythema) improved during the study in each group, without any statistical difference.

At V1, 77 cases did not have a bacterial pathogen isolated from a culture swab. The most prevalent pathogens were *Staphylococcus intermedius* (97 strains, 50 in Orbimax group and 47 in Surolan group), *Streptococcus β-haemolyticus* (23 strains, 15 Orbimax group and 8 in Surolan group), *Pseudomonas aeruginosa* (18 strains, 11 Orbimax group and 7 in Surolan group), *Enterococcus spp.* (15 cases, 7 Orbimax group and 8 in Surolan group), *Escherichia coli* (10 strains, 8 Orbimax group and 2 in Surolan group) and *Proteus mirabilis* (10 strains, 6 Orbimax group and 4 in Surolan group).

At V2, bacterial success rates for these 6 most prevalent pathogens were not significantly different between the Orbimax group and Surolan group:

- below 40% of cure rate (CR) for *Staphylococcus intermedius* in both groups,
- near 80% of CR for *Streptococcus β-haemolyticus*,
- near 50% of CR for *Pseudomonas aeruginosa,*
- 100% of CR for *Enterococcus spp.* and *Escherichia coli* in the Orbimax group, and respectively 65% and 50% in the Surolan group,
- 80% of CR for *Proteus mirabilis* in the Orbimax group and 100% in the Surolan group.

Comparison between pre- and post-treatment orbifloxacin MICs distribution indicated that the orbifloxacin MIC for the major pathogens, *Staphylococcus intermedius*, did not show any trend of increasing after Orbimax therapy.

Microbiological success for yeast based on cytology was not statistically significantly different between treatment groups: 57.1 % success rate in Orbimax group and 54.8% in Surolan group.

Investigator and owner overall outcome evaluations were better in the Orbimax group than in the Surolan group; only statistically significant (p=0,0001) for investigator overall outcome evaluation.

Five adverse reactions were reported. Two are not really adverse reactions: one dog was run over by a car 3 days after initiation treatment in Orbimax group, and one owner was not compliant with Orbimax formulation ("too fatty, oily and not easy to apply"). Vomiting was reported in one case in each group, and head-shaking in one Surolan-treated dog.

Discussion

This pivotal clinical study was well conducted. The trial, with comparison to a similar product, confirms the clinical efficacy of the test product when compared to a registered one (Surolan).

A statistical analysis was performed on all cases, which had been confirmed for both bacterial and fungal contaminations; however, it was confirmed that all enrolled cases at V1 had clinically significant *Malassezia infection*. In veterinary practice, dogs may be treated according to clinical symptoms and results of a roll smear, without a laboratory confirmation.

The applicant was asked to comment on the timing of the post-treatment microbiology sampling as clinical experience suggests that otic preparations remain in the ear for a few days after the end of treatment. The applicant explained that microbiological growth was not artificially retarded by residual material based on the fact that normal flora (*Staphylococcus intermedius*) was readily cultured post-treatment.

It was also noted that the microbiological "cure rate" included cases where the pre-treatment pathogen was reduced in quantity post-treatment, rather than just those cases for which the pathogen was eliminated. The "cure rates" were rediscussed at the request of the Committee. The applicant argued that the most meaningful endpoints for a field study of canine otitis externa are clinical, not microbiological. The recovery of normal flora, such as *Staphylococcus intermedius*, post-treatment is not unexpected. In fact, it is reassuring that the ear canal is not "sterilised" by the topical treatment as this may proceed to a superinfection. The timing of post-treatment sampling should be carefully justified to take account of the time taken for the normal flora to re-establish.

The applicant was also asked to indicate if bacteria cultured at Day 0 were pathological or part of the commensal flora in these field trials. The applicant responded that in otitis externa, the line between pathogen and commensal organism is blurred. For example, the most common organisms isolated from ears of dogs afflicted with otitis externa are part of the normal flora, i.e., *Staphylococcus intermedius* and *Malassezia pachydermatis*. The ear canal of most normal dogs harbours low numbers of a variety of commensal and potentially pathogenic bacteria. Commensal and pathogenic bacteria quickly colonise an ear canal whose lining or microclimate has been altered. CVMP acknowledged that it can be difficult to determine the pathogenic significance of isolates from cases of otitis externa. For this reason, cytological examination is frequently performed to broadly identify the type of organism present, and to look for the presence of leucocytes and phagocytosis of bacteria which would indicate pathogenicity of organisms. Cytology was not performed in this field study, and it would be difficult to determine the pathogenic significance of the isolates retrospectively.

The CVMP considers that it is of importance to establish microbiological cure rates for products with antimicrobial claims (reference to guideline EMEA/CVMP/627/01). As these were difficult to clearly establish in the clinical trials, it was decided not to include target pathogens in the indications for the product.

The study statistics demonstrate that a high proportion of cases of otitis externa (> 50%) are recurrent/chronic. For both field studies the criteria on which (recurrence/duration) otites were divided into acute, recurrent or chronic was specified at the request of the Committee. It was included on the 'case history and physical exam form'.

Failing to treat cases for a sufficient period of time can also encourage antimicrobial resistance. Guideline EMEA/CVMP/627/01 states that for clinical endpoints, post-treatment follow-up should be performed for sufficient time after the effects of treatment would be expected to have ceased. The potential for clinical relapse following the proposed treatment regimen was investigated at the request of the Committee. There were only 4 Posatex cases and 5 Surolan cases that were not clinical successes by Day 8 in the field study. The individual clinical scores were provided for these 9 cases.

The applicant commented that the clinical relapse rate will depend on the primary and predisposing causes that give rise to the otitis externa, and that it was beyond the scope of the trial to assess the success of a 7 day intervention with Posatex to see if chronic follow up care was successful. The trial duration was therefore designed to investigate only acute otitis externa, although recurrent/chronic cases were also recruited. According to the study report, 19.9 % of enrolled cases had a history of a dermatological disorder (atopic dermatitis and flea allergy dermatitis were most frequent). Although it may have been difficult to assess for relapse in these cases, follow up for the remaining cases would have been useful and would have helped to justify the 7-day treatment period for acute cases, and proposed extended duration of treatment as suggested by the applicant. The investigation for relapses should have been undertaken, especially since no dose determination or dose confirmation studies have been presented.

In the field trials, dogs were only treated for 7 days. The systemic and local effects (HPA suppression, skin atrophy etc) may be exaggerated in clinical cases where inflamed tissues with damaged barrier function may absorb substantially more of the active substances.

Following discussions and detailed review of the available data, the use of the product was confined to acute and recurrent cases. Even though current practice may consist of treatment periods that go

beyond 7 days, it was decided that there was no data to confirm that this would result in improved efficacy, and the treatment period should therefore be limited to 7 days. As there is inadequate long term safety and efficacy data from the field trials to support treatment of chronic otitis this indication was refused.

Prudent use guidelines suggest that fluoroquinolones should in general not be used as a first-line treatment for acute infections. The indication for the treatment of acute otitis was accepted provided the following warning was added to the SPC section 4.5: "Use of the product should be based on susceptibility testing of isolated bacteria, and/or other appropriate diagnostic tests."

Other studies

Biofilm can be a key factor of inefficiency or failure of treatment. No study was conducted for evaluation of interaction of Posatex with commercial ear cleaner solutions. A statement to that effect is included in the SPC section 4.8.

For the oral explanation, a comparative study was submitted that evaluated the impact on the hypothalamic-pituitary-adrenal cortex axis in dogs over 14 days of treatment. There is some indication that the glucocorticosteroid component of Posatex, mometasone, has less suppressive impact than other glucocorticosteroids over this time period. However, the study should be considered as indicative, rather than pivotal, as questions remain about the study design. For example, it was not clear if the dose tested was high enough to be of the same order as the one used in the field.

Overall conclusion on efficacy

Posatex has shown to be efficacious in a number of studies. This type of combination of active substances can be considered as occupying a well-established place in veterinary medicine.

The strengths of the product lie in the choice of active substances whose pharmacodynamics are particularly adapted to the treatment of bacterial ear infection. Orbifloxacin is a fluoroquinolone antibiotic. Posaconazole has antifungal as well as antibacterial activity. Mometasone is a potent glucocorticosteroid.

Given the local use of the product, resistance is not expected to be a problem. Even though the doses are likely to be high in terms of efficacy, they are well tolerated. Dose optimisation is considered a difficult exercise for this type of product, applied locally in dog ears. Orbifloxacin is a fluoroquinolone and though resistance is not expected to be a problem, particular caution is warranted. Likewise, mometasone is a very strong glucocorticosteriod. In this case prolonged treatment could lead to classic side-effects as mometasone is absorbed in the ear canal. The fact that there is some indication that mometasone does not suppress the HPA axis to the same extent as other glucocorticoids, while having potent anti-inflammatory activity is reassuring.

The protocol explains under which criteria (recurrence / duration) otitis have been divided into acute, recurrent or chronic. The study was designed only to investigate treatment duration of 7 days, with no provision to monitor for relapse. Even though current practice may consist of treatment periods that go beyond 7 days in many cases, it was decided that based upon the available field data the maximum treatment period should be limited to 7 days.

Long-term target animal safety and efficacy data from the field trials were inadequate to support treatment of chronic otitis. The use of the product was therefore restricted to the treatment of acute or recurrent cases. Warning sentences also include risk mitigation measures in regards to antibiotic treatment, which are considered essential here.

5. RISK BENEFIT BALANCE

Benefit assessment

Direct benefit

Posatex 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.

Posatex 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 2 years and an in-use shelf-life of 28 days has 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.

Indirect benefit

Ear drop suspensions are easy to apply by the owner and hence increased success rate in the treatment of ear infection overall can be expected because of greater compliance.

Other benefits

Two new substances (posaconazole and mometasone) in veterinary medicine are to be authorised in this product increasing the range of products available

Risk assessment

The use of a fluoroquinolone and the potential for resistance was considered a concern. However, it is not expected that there will be increased emergence of fluoroquinolone resistance with the topical use as indicated for Posatex.

Ototopical use of posaconazole is directed at controlling *Malassezia* and a supraoptimal concentration of posaconazole is applied directly to the site of infection. The concentration of posaconazole within Posatex is 850X the MIC_{90} and resistance is unlikely to be induced.

The use of a potent glucocorticosteroid is of concern. However a comparative study provided some indication of the impact on the hypothalamic-pituitary-adrenal cortex axis in dogs over 14 days of treatment. There is some indication that the glucocorticosteroid mometasone, has less suppressive impact than other glucocorticosteroids over this time period.

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 7 day course of treatment as indicated in the pivotal field study, however, this may not be sufficient in all cases of otitis externa. It was not possible to approve a longer course of treatment in the absence of supporting data, however, CVMP recognised that veterinarians may need to continue treatment beyond 7 days. It was considered that such an extension is unlikely to compromise safety.

In the absence of robust data against the efficacy of specific pathogens it was agreed to exclude the mention of specific pathogens from the indication but to provide general information in section 5.1 Pharmacodynamic properties of the SPC.

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 4.8 that the ear canal should be cleaned before application of the product.

Two new active substances in veterinary medicine are authorised in this product and while safety has been demonstrated, there is limited clinical experience in the field.

The product is to be stored in a refrigerator at (2 °C – 8 °C) and there is a risk that compliance may be a problem.

No materials of animal origin are contained or used in this veterinary medicinal 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 Posatex 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. Posatex has been shown to be efficacious for the indication 'Treatment of acute otitis externa and acute exacerbations of recurrent otitis externa, associated with bacteria susceptible to orbifloxacin and fungi susceptible to posaconazole, 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 Posatex were considered to be in accordance with the requirements of Council Directive 2001/82/EC as amended.