CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Cetraxal 2 mg/ml ear drops, solution SALVAT S.A., Spain

ciprofloxacin (as hydrochloride)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1420/001/DC
Registration number in the Netherlands: RVG 102959

17 March 2011

Pharmacotherapeutic group:	otologicals, antiinfectives
ATC code:	S02AA15
Route of administration:	auricular
Therapeutic indication:	acute otitis externa in patients with an intact tympanic membrane, caused by ciprofloxacin susceptible microorganisms in adults and children older than 1 year
Prescription status:	prescription only
Date of authorisation in NL:	6 January 2011
Concerned Member States:	Decentralised procedure with DE, EL, FR, IT, UK
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Cetraxal 2 mg/ml ear drops, solution as single dose ampoule from SALVAT S.A. The date of authorisation was on 6 January 2011 in the Netherlands. The product is indicated for the treatment of acute otitis externa in patients with an intact tympanic membrane, caused by ciprofloxacin susceptible microorganisms in adults and children older than 1 year.

A comprehensive description of the indications and posology is given in the SPC.

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.
In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

This decentralised procedure concerns a full application based on article 8(3) of Directive 2001/83/EC.
The product registered on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain.

Considering the indication applied for, the main focus of the non-clinical dossier are systemic exposure, ototoxicity and local tolerance. Apart from an overview of relevant studies from literature, the MAH has conducted some additional studies in relation to the route of administration.
The clinical development program for Cetraxal 2 mg/ml ear drops solution includes one pivotal multicenter study of safety and efficacy (CIPROT III/03 IA 02). This pivotal study plus a study described in Pistorius, Westberry, Drehobl, et al., 1999 are referred to as the Core Studies. Study CIFLOT III/00-01 is referred to as the supportive study. Additional information has been found in several Published Studies of ciprofloxacin otic solution at concentrations of 0.2%, 0.3%, and 0.5%.
The overview on the clinical pharmacology, efficacy and safety provided by the MAH gives a reasonable review of these issues concerning Cetraxal 2 mg/ml ear drops solution. Report refers to 64 publications up to the year 2005. Most clinically relevant publications are from the 90s and earlier.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted. The MAH adapted the product information in accordance with the EU Worksharing procedure on paediatric data for Ciloxan eye- and eardrops.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ciprofloxacin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a pale yellow, slightly hygroscopic crystalline powder, which is soluble in water, slightly soluble in methanol, very soluble in ethanol, and practically insoluble in ethyl acetate and methylene chloride. The active substance does not exhibit polymorphism or isomerism.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The Ph.Eur. specifications/analytical methods and the additional specifications/analytical methods as included on the CEP for drug substance are adopted. Batch analysis results have been provided, demonstrating compliance with the specification.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Cetraxal is a clear, sterile, preservative-free aqueous solution with pH 4.0-5.0 and osmolality of 270-328 mOsm/kg.

The solution is packed in a formed low-density polyethylene (LDPE) ampoule. Each single ampoule delivers 0.25 ml dropwise. The ampoules are contained in an aluminium foil overwrap pouch for protection.
Each single-dose ampoule delivers 0.25 ml of solution that contains 0.58 mg of ciprofloxacin hydrochloride monohydrate corresponding to 0.50 mg of ciprofloxacin.

The excipients are: povidone (E1201), glycerine (E422), purified water (E270), sodium hydroxide (E524) and lactic acid (for pH-adjustment).

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The basis of the development of the formulation is the osmolality of the solution. The drug product was based on the product developed for the American market. Suitability of the semi-permeable container has been demonstrated by weight loss study and a validated extractable leachability study with the USA packaging material, which has been demonstrated to be similar to the packaging materials used by the proposed manufacturing site.

A solution loss on dispensing study has been performed to determine the required fill volume for the ampoules to ensure a delivered volume of 0.25 ml. The study report has been provided and supports the fill target of 0.30 ml. No overage is used.

The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The drug product is manufactured as a sterile solution using blow-fill-seal technology. After preparation of the solution, it is filtered through a micron filter into holding tanks, followed by sterile filtration into the filling machine. The ampoules are moulded, filled and sealed in a continuous process.

The manufacturing process is considered a non-standard process in view of the aseptic filtration and processing and the low content of active substance. The manufacturing process has been validated according to relevant European guidelines with three full-scale batches.

Control of excipients

The excipients comply with Ph.Eur.These specifications are acceptable.

Microbiological Attributes

The drug product is manufactured as an aseptically filtered single dose unit and rendered sterile. The bulk solution is passed through a micron filter into the holding tank and again through a micron filter before filling. The ampoules are directly sealed after filling. Sterility is tested at release and during stability. Since the drug products concern single dose units, no preservatives are added.

Quality control of drug product

The product specification includes tests for identity, pH, osmolarity, color, clarity, uniformity of dosage units, viscosity, assay, related substances and sterility. The release and shelf-life specification are identical except for the tighter release limits for pH and the wider upper shelf-life limit for assay. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three production-scale batches, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full-scale batches, manufactured at one site, stored at 25°C/60%RH (36 months) and 40°C/75%RH (6 months) and two full-scale batches from another site stored at 25°C/60%RH (18 months) and 30°/65%RH (12 months) and 40°C/NMT 25%RH (6 months) and 2-8°C (18 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in PE vials in aluminium pouch. Placement of additional production-scale batches on stability studies has been committed.

The stability data of the batches demonstrate an increase in weight loss and assay and a slight increase in impurities and osmolality. Beside this, no obvious trends could be observed. Both batches from the second manufacturer demonstrate out of specification results for pH in the accelerated stability study. The increase in assay was related to the increase in weight loss rather than degradation. Therefore, the widened shelf-life limit for assay can be accepted. The release limits for pH have been tightened to ensure future compliance with the specifications. Statistical analysis has been performed.

Supported by the updated stability data, the presented statistical analysis, the explanations and the revised limits for assay and pH, the extrapolation of 6 months is deemed justified in line with ICH Q1A(R2). Based on the stability data the proposed shelf life of 24 months can be granted. The drug product should be stored below 30°C in the original package in order to protect from light according to the

Ph.Eur monograph. Additional stability data up to the claimed shelf-life of 24 months should be submitted when available.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

In support of the application, the MAH submitted an overview of relevant studies from literature. Additionally the MAH has conducted some additional studies in relation to the route of administration: a study on repeat dose toxicity after topical administration, and two local toxicity studies.

Good Laboratory Practice
The GLP status of many of the literature based non-clinical studies along with compliance with the ICH guidelines is unknown. However, the two pivotal topical toxicology studies conducted by SALVAT to evaluate repeat dose/local tolerance toxicity and local skin tolerance using guinea pigs and rabbits, respectively, were conducted under GLP conditions.

Pharmacology
Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. In the large majority of cases of infection, *Pseudomonas aeruginosa* (and occasionally *Staphylococcus aureus*) is the pathogen, and both have a high susceptibility to ciprofloxacin. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.
The safety and efficacy of ototopical ciprofloxacin hydrochloride (0.2%) in the treatment of experimental chronic suppurative otitis media caused by *Pseudomonas aeruginosa* infection was assessed in cynomolgus monkeys. 0.2% ciprofloxacin did not cause hearing loss and no monkeys showed any significant morphological changes in the outer hair cells. 0.2% ciprofloxacin also showed efficacy in eradicating the infectious agent, *P aeruginosa.* This eradication did not always correlate to the resolution of ear drainage.
Relevant summaries of safety pharmacology literature for cardiovascular and central nervous system (CNS) effects after intravenous exposure have been included for completeness. There were no published studies of the potential pulmonary effects. Ciprofloxacin has known CNS effects after systemic exposure, which is exacerbated by the use of certain anti-inflammatory drugs. In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg. The levels needed to cause clonic tonic seizures or convulsions would never be achieved after exposure to Ciprofloxacin Otic Solution 0.2%.
The administration of certain fluoroquinolones with specific structural characteristics (grepafloxacin and sparfloxacin) has been shown to cause a dose dependent increase in QT intervals, which is thought to contribute to the generation of the ventricular arrhythmia torsades de pointes. Blockade of voltage dependent K+ channels (HERG) in the human heart is thought to contribute to the prolongation of repolarization and arrhythmias. Ciprofloxacin has not shown to cause these effects. Ciprofloxacin was tested for HERG channel inhibition and action potential duration prolongation in transfected Chinese hamster ovary cells and guinea pig ventricular myocardia, *in vitro.* Systemic exposure after administration of the recommended dose of Ciprofloxacin Otic Solution 0.2% is anticipated to be below that associated with cardiovascular effects.

Pharmacokinetics

The MAH has been demonstrated that absorption after topical administration is negligible, and therefore no further studies on the pharmacokinetics of this product were conducted.

Toxicology
Considering the indication applied for, the main focus of the toxicology dossier is ototoxicity and local tolerance. Apart form an overview of relevant studies form the public literature, the MAH has conducted one repeat dose toxicity study using otic administration, and two local tolerance tests. For the repeat dose toxicity study and one of the local tolerance tests, a different product was used, containing also fluocinolone. These studies showed some adverse effects, including with mild focal mononuclear infiltrates, and slight erythema, but it is not clear whether these effects are due to ciprofloxacin, fluocinolone or other excipients present in the formulation. However, the weight of evidence, including the negative dermal irritation study and negative repeat dose ototoxicity studies from public literature, it is unlikely that ciprofloxacin otic solution 0.2% will cause adverse effects in the ear.
The toxicity profile of ciprofloxacin due to systemic exposure is well known. The main areas of toxicological concern include nephrotoxicity due to crystal formation in urine, arthropathy, chondrotoxicity, and CNS effects. Of the eight different *in-vitro* genotoxicity assays performed, two results were positive. These results concur with those summarized from a review of ciprofloxacin mutagenicity. Ciprofloxacin was tested in the rat hepatocyte DNA repair assay, mouse micronucleus test and the mouse dominant lethal test. Results where negative in all *in-vivo* assays of genotoxicity. Carcinogenicity studies and reproduction studies were negative for ciprofloxacin, although these results are not relevant for the current application due to the negligible absorption after topical administration.

Local tolerance
Two local tolerance tests were performed by the MAH. The non-GLP study used 0.3% ciprofloxacin, while the GLP study used ciprofloxacin 0.3% + fluocinolone acetonide 0.025%. The results of the latter study can therefore not be extrapolated to the product for which marketing authorization is sought for. Even though it seems unlikely that the fluocinolone present in the solution is the cause of the dermal irritation observed, other excipients that are present in this formulation but not in the formulation applied for, might be the cause. In light of the weight of evidence, including the negative dermal irritation study and negative repeat dose ototoxicity studies from public literature, it is unlikely that ciprofloxacin otic solution 0.2% will cause adverse effects in the ear.

Environmental risk assessment
A 'worst case scenario' of two infected ears would result in a daily dose of 2 mg. The $PEC_{surface\ water}$ would then be 0.1 µg/ml. Although this is the threshold for phase II testing, it has to be taken into account that this product should only be used for 7 consecutive days. Therefore, a slight modification of the daily dose in the calculation results in a $PEC_{surface\ water}$ below the trigger value. Phase II testing is therefore not considered necessary, and the product is unlikely to present a risk to the environment.

II.3 Clinical aspects

Quality of clinical studies, compliance with GCP
The clinical studies contained in the dossier are stated to have been carried out in line with the ethical priniciples of Good Clinical Practice (GCP) and in accordance with the Declaration of Helsinki.

Pharmacokinetics
No bioavailability or bioequivalence studies were conducted, as Cetraxal 2 mg/ml ear drops solution is locally acting product. This can be accepted, also since the absorption in the non-clinical studies was negligible.

Pharmacodynamics
Because of the extent of pharmacology data already available, the MAH did not conduct clinical pharmacology studies of Cetraxal 2 mg/ml ear drops solution to support this application. The mechanism of action of ciprofloxacin is well known.

Clinical efficacy

The clinical development program for Cetraxal 2 mg/ml ear drops solution includes one pivotal multicenter study of safety and efficacy (CIPROT III/03 IA 02). This pivotal study plus a study described in Pistorius, Westberry, Drehobl, et al., 1999 are referred to as the Core Studies. Study CIFLOT III/00-01 is referred to as the supportive study. Additional information has been found in several Published Studies of ciprofloxacin otic solution at concentrations of 0.2%, 0.3%, and 0.5%.

Pivotal study CIPROT III/03 IA 02

In total 630 patients from 2 years of age with clinically diagnosed OE were enrolled at 47 study centers in the US and Spain in an open and randomized study: 318 to the test product Cetraxal 2 mg/ml ear drops solution group and 312 to the PNH (Polymyxin B sulfates, Neomycin and Hydrocortisone) group. The test product was supplied in single-dose vials, each vial containing 0,25 mL (0.50 mg ciprofloxacin), and was administered BID for 7 days. PNH was administered 4 drops TID (for patients who were over 12 years of age, i.e., had reached their thirteenth birthday) or 3 drops TID (for patients who were 12 years of age or younger, *i.e.* had not reached their thirteenth birthday) in the affected ear canal for 7 days.

Summary of the pivotal efficacy study is tabulated below:

Table 2.7-26 Summary of Clinical Efficacy Studies

Study identification	Study design	Patient population	Concentration of otic ciprofloxacin	Volume and frequency of application of otic ciprofloxacin	Treatment duration for otic ciprofloxacin	Comparator treatment	Efficacy summary
Core Studies							
Pivotal Study: CIPROT III/03 IA 02.[5]	Randomized, active-controlled, parallel-group, evaluator-blinded, multicenter	630; 627 included in CITT population (318 ciprofloxacin: 175 M, 143 F, aged 2-83)	0.2%	0.25 mL *bid*	7 days	PNH 4 drops *tid* for patients over 12, 3 drops *tid* for patients 12 years or younger	Clinical Cure at Visit 4: CPP population: 214 (87%) with ciprofloxacin, 197 (81%) with PNH CITT population: 259 (81%) with ciprofloxacin, 237 (77%) with PNH. Proportions of patients with Clinical Cure at Visit 3, Clinical Improvement at Visit 3 and at Visit 4, and Clinical + Microbiological Cure at Visit 3 and at Visit 4 were generally greater for ciprofloxacin than for PNH. Proportions of patients with resolution of otalgia and improvement in otalgia at Visit 3 and at Visit 4 were generally similar between ciprofloxacin and PNH.

Main inclusion/diagnosis criteria: Male and female patients aged at least 2 years who had acute diffuse otitis externa (OE) of less than 3 weeks' duration. Patients were excluded if they used prohibited concomitant medications (including other investigational treatments, other treatments for OE, or other antibiotics), or if they had a history of adverse reaction to any component of either study medication; had complicating conditions (including otic dermatitis, eardrum perforation, tympanostomy tubes, otomycosis, mastoid disease, diabetes, or immunodeficiency).

Study design: Patients were randomized and started treatment at Visit 1 (Day 1).
The End of Treatment (EOT) visit 3 occurred between Day 8 and Day 10, or within 2 days after premature discontinuation of study treatment.
The test-of-cure (TOC) visit 4 at which final efficacy and safety assessments were made occurred between Day 15 and Day 17.
Clinical outcomes at EOT and TOC were classified as Clinical Cure, Clinical Improvement, Clinical Failure, or Indeterminate.

Microbiological Efficacy Parameters: At Visits 1, 3, and 4, if ear discharge was present, samples were to be cultured and pathogens identified according to standardized microbiological methods. Bacteriologic responses at Visits 3 and 4 were classified as Eradication, Presumed Eradication, Persistence, Presumed Persistence, Superinfection, or Indeterminate.

Clinical + Microbiological Efficacy cure: otalgia, edema, and otorrhea were resolved and bacteriological response was Eradication or Presumed Eradication.
Clinical + microbiological improvement was considered achieved if otalgia, edema, and otorrhea were improved or resolved and bacteriological response was Eradication or Presumed Eradication.

Primary Efficacy Endpoints were: proportions of patients in the Clinical Per-Protocol (CPP) population (All patients in the CITT population who had none of the following protocol deviations: violation of any of the inclusion or exclusion criteria) and Clinical Intent-to-treat (CITT) population (All randomized patients who received at least 1 dose of study medication) with clinical cure at Visit 4.

Secondary Efficacy Endpoints: clinical cure at Visit 3; clinical improvement at Visit 3 and at Visit 4; resolution of otalgia at Visit 3 and at Visit 4; improvement in otalgia at Visit 3 and at Visit 4; clinical + microbiological cure at Visit 3 and at Visit 4; and clinical + microbiological improvement at Visit 3 and at Visit 4.

Statistical Methods: 95% confidence interval (CI) was used to test that Cetraxal 2 mg/ml ear drops solution was non-inferior to PNH. The non-inferiority margin of 10% was chosen based on historical precedent for this disease and prior clinical trials non-inferiority was claimed if the clinically meaningful difference of 0.10(10%) was greater than the upper limit of the 95% CI.

Clinical failure: patients with clinical cure or clinical improvement at visit 3 but worsening between visit 3 and visit 4 were considered clinical failure at visit 4.

Results
Clinical cure at visit 4: In the CPP population, 214 (86.6%) patients in the ciprofloxacin group and 197 (81.1%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups was -5.6% (95% CI -12.1%, 0.9%). In the CITT population, 259 (81.4%) patients in the ciprofloxacin group and 237 (76.7%) in the PNH group had Clinical Cure at Visit 4. The difference between treatment groups was -4.7% (95% CI -11.1%, 1.6%).

For more details see the tables below:

Table 2.7-6 Clinical Cure at Visit 4 in Study CIPROT III/03 IA 02: CPP Population

	Number (%) of Patients		Treatment Difference
	Ciprofloxacin (N=247)	PNH (N=243)	(PNH-ciprofloxacin) with 95% CI
Clinical Cure	214 (86.6)	197 (81.1)	-5.6 (-12.1, 0.9)*
Sustained Clinical Cure	170 (68.8)	140 (57.6)	
Subsequent Clinical Cure	44 (17.8)	57 (23.5)	
Clinical Failure	33 (13.4)	46 (18.9)	

* Meets the protocol criteria for non-inferiority.

Table 2.7-7 Clinical Cure at Visit 4 in Study CIPROT III/03 IA 02: CITT Population

	Number (%) of Patients		Treatment Difference
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Clinical Cure	259 (81.4)	237 (76.7)	-4.7 (-11.1, 1.6)*
Sustained Clinical Cure	208 (65.4)	171 (55.3)	
Subsequent Clinical Cure	51 (16.0)	66 (21.4)	
Clinical Failure	59 (18.6)	72 (23.3)	
Indeterminate	14 (4.4)	11 (3.6)	

* Meets the protocol criteria for non-inferiority.

The upper limit of the 95% CI, 0.9% in CPP population and 1.6% in CITT population, was smaller than the predefined limit of 10%; thus, ciprofloxacin was non-inferior to PNH in the both CPP and CITT populations.
Furthermore, the Clinical failure was 33 (13.4%) in ciprofloxacin group and 46 (18.9%) in comparator group for CPP population. For CITT population, that was 59 (18.6%) in ciprofloxacin group and 72 (23.3%) in PNH group. 4.4% vs 3.6% respectively in ciprofloxacin and PNH groups were indeterminate.

Clinical cure at visit 3: As expected, fewer patients had Clinical Cure at Visit 3 than at Visit 4. In the CPP population, the proportions were 70% (173) for the ciprofloxacin group and 60.5% (147) for the PNH group {-9.5 (-17.9, -1.2)}. In the CITT population, the proportions were 67.3% (214) and 59.2% (183) with a treatment difference of -8.1 (-15.6, -0.5). The clinical failure was approximately 30-40% in the treatment groups. Most of outcomes classified as clinical failure were clinical improvements. In the CITT population, 4% in ciprofloxacin and 2.9% in PNH groups were indeterminate.

Clinical improvement at visit 3 and visit 4: In both populations, the large majority of patients assessed at both visits had Clinical Improvement. Clinical Improvement in the ciprofloxacin group was greater (92.7% and 89.5%) than that in the PNH group (88.5% and 83.1%) at Visit 3 and 6 percentage points at Visit 4 in CPP population. The treatment differences were -3.6 (-8.8, 1.7) at visit 3 and -5.6 (-11.7, 0.4) at visit 4.

Resolution of otalgia and improvement in otalgia at Visit 3 and at Visit 4: In the CPP population, 87.4% in ciprofloxacin group and 88.1% in PNH group reported resolution of otalgia at Visit 3, and 96.4% in the ciprofloxacin group and 97.1% in the PNH group reported resolution or improvement.

At Visit 4, 96% in ciprofloxacin group and 97.1% in PNH group reported resolution of otalgia, and almost all reported resolution or improvement in the CPP population.
Results in the CITT population were similar to those in the CPP population. See the table below:

Table 2.7-13 Clinical Outcome for Otalgia at Visit 3 and Visit 4 in Study CIPROT III/03 IA 02: CITT Population

	Number (%) of Patients		Treatment Difference
	Ciprofloxacin (N=318)	PNH (N=309)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Number of patients	306	301	
Resolved	271 (88.6)	260 (86.4)	-2.2 (-7.4, 3.1)
Improved	24 (7.8)	27 (9.0)	
Resolved or improved	295 (96.4)	287 (95.3)	-1.1 (-4.2, 2.1)
Not resolved or improved	11 (3.6)	14 (4.7)	
Visit 4			
Number of patients	305	300	
Resolved	294 (96.4)	289 (96.3)	-0.1 (-3.0, 2.9)
Improved	6 (2.0)	6 (2.0)	
Resolved or improved	300 (98.4)	295 (98.3)	-0.0 (-2.1, 2.0)
Not resolved or improved	5 (1.6)	5 (1.7)	

Clinical + Microbiological Cure and Improvement at Visit 3 and at Visit 4: for the Microbiological Per-Protocol (MPP) population, at Visit 3, 69.5% in ciprofloxacin group and 59.8% in PNH group had both Clinical + Microbiological Cure with a treatment difference of -9.8(-19.8, 0.2). Clinical + Microbiological Improvement was observed in 21.3% in ciprofloxacin group and 25.9% in PNH group. Failure was reported 16(9.2%) vs 25(14.4%) in ciprofloxacin and PNH groups respectively. These results are tabulated below:

Table 2.7-14 Clinical + Microbiological Outcome at Visit 3 and Visit 4 in Study CIPROT III/03 IA 02: MPP Population

	Number (%) of Patients		Treatment Difference
	Ciprofloxacin (N=174)	PNH (N=174)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Cure	121 (69.5)	104 (59.8)	-9.8 (-19.8, 0.2)
Improvement	37 (21.3)	45 (25.9)	
Failure	16 (9.2)	25 (14.4)	
Visit 4			
Cure	148 (85.1)	136 (78.2)	-6.9 (-15.0, 1.2)
Improvement	5 (2.9)	3 (1.7)	
Failure	21 (12.1)	35 (20.1)	

At Visit 4, Clinical + Microbiological Cure had increased to 85.1% in ciprofloxacin group and 78.2% in PNH group. Clinical + Microbiological Improvement at Visit 4 were 2.9% in the ciprofloxacin group and 1.7% in the PNH group. Failure was 21(12.1%) in ciprofloxacin group and 35(20.1%) in PNH group.

Clinical + microbiological outcomes for the Microbiological Intent-to-treat (MITT) population were generally similar to those in the MPP, as shown in the table below:

Table 2.7-15 Clinical + Microbiological Outcome at Visit 3 and Visit 4 in Study CIPROT III/03 IA 02: MITT Population

	Number (%) of Patients		Treatment Difference
	Ciprofloxacin (N=232)	PNH (N=217)	(PNH-ciprofloxacin) with 95% CI
Visit 3			
Cure	153 (65.9)	129 (59.4)	-6.5 (-15.4, 2.4)
Improvement	48 (20.7)	53 (24.4)	
Failure	31 (13.4)	35 (16.1)	
Visit 4			
Cure	184 (79.3)	163 (75.1)	-4.2 (-12.0, 3.6)
Improvement	8 (3.4)	5 (2.3)	
Failure	40 (17.2)	49 (22.6)	

At Visit 4, Clinical + Microbiological Cure had increased to 79.3% in ciprofloxacin group and 75.1% in PNH group {treatment difference: -4.2(-12.0, 3.6)}, and Clinical + Microbiological Improvement were 3.4% in ciprofloxacin group and 2.3% in PNH group. Failure was 17.2% vs 22.6% in the test and comparator groups.
The results of clinical and microbiological cure and improvement wee less pronounced, however, ciprofloxacin presents better results in comparison with the comparator.

Clinical cure by pathogen: the primary efficacy analysis and selected secondary analyses were performed by pathogen. Because of the small number of patients with other pathogens, analyses were performed for *P.aeruginosa* and *S. aureus* only.
For more details see the table below:

Table 16 Common Pathogenic Organisms Isolated from Cultures at Baseline: MPP Population

Pathogens Isolated from at Least 8 Patients

	Number (%) of Patients with Pathogen	
	Ciprofloxacin (N=174)	PNH (N=174)
Number of patients with any pathogen*	174	174
Pseudomonas aeruginosa	152 (87.4)	154 (88.5)
Staphylococcus aureus	22 (12.6)	29 (16.7)
Enterobacter cloacae	10 (5.7)	3 (1.7)
Klebsiella pneumoniae	8 (4.6)	6 (3.4)
Escherichia coli	6 (3.4)	6 (3.4)
Klebsiella oxytoca	5 (2.9)	3 (1.7)

* There could be more than 1 pathogen from a single patient.
Source: Statistical Table 20.1.1.

The results in MITT population were similar to those in MPP population. See the table below:

Table 17 Common Pathogenic Organisms Isolated from Cultures at Baseline: MITT Population

Pathogens Isolated from at Least 8 Patients

	Number (%) of Patients with Pathogen	
	Ciprofloxacin (N=232)	PNH (N=217)
Number of patients with any pathogen*	232	217
Pseudomonas aeruginosa	197 (84.9)	193 (88.9)
Staphylococcus aureus	33 (14.2)	35 (16.1)
Klebsiella pneumoniae	12 (5.2)	6 (2.8)
Enterobacter cloacae	12 (5.2)	5 (2.3)
Klebsiella oxytoca	8 (3.4)	5 (2.3)
Escherichia coli	7 (3.0)	6 (2.8)
Enterobacter aerogenes	5 (2.2)	3 (1.4)

* There could be more than 1 pathogen from a single patient.
Source: Statistical Table 20.1.2.

Because of the higher sensitivity of *P.aeruginosa* to ciprofloxacin, the results were more pronounced in the both treatment groups and slightly lower for *S. aureus.*

Bacteriologic response: in the MPP population, at both visit 3 and visit 4, the bacteriologic response was eradication or presumed eradication for the great majority of patients in both treatment groups.
For more details see the table below:

Table 18 Bacteriologic Response: MPP Population

		Number (%) of Patients	
		Ciprofloxacin (N=174)	PNH (N=174)
Visit 3	Number of patients	174	174
	Eradication	39 (22.4)	46 (26.4)
	Presumed Eradication	128 (73.6)	115 (66.1)
	Eradication or Presumed Eradication	167 (96.0)	161 (92.5)
	Persistence	1 (0.6)	5 (2.9)
	Presumed Persistence	5 (2.9)	8 (4.6)
	Superinfection	1 (0.6)	0
Visit 4	Number of patients	174	174
	Eradication	16 (9.2)	22 (12.6)
	Presumed Eradication	141 (81.0)	130 (74.7)
	Eradication or Presumed Eradication	157 (90.2)	152 (87.4)
	Persistence	1 (0.6)	1 (0.6)
	Presumed Persistence	16 (9.2)	21 (12.1)
	Superinfection	0	0

Source: Statistical Table 21.1.1.

In the MITT population, trends were generally similar to those in the MPP population and 4% in the ciprofloxacin group and 2% in the PNH group were assessed as indeterminate.

Supportive data

The supportive study (CIFLOT III/00-01), a multicentre, randomised, parallel-group, double-blind clinical trail to evaluate the clinical efficacy of 0.3% ciprofloxacin ear drops plus fluocinolone 0.025% compared with the use of 0.3% ciprofloxacin alone in the treatment of diffuse otitis externa. In total 590 patients aged 7 years and older, with a diagnosis of diffuse OE were included at 33 study centers in Spain: 296 of these were randomized to Cetraxal Plus (ciprofloxacin 0.3% plus fluocinolone 0.025%), and 294 were randomized to the ciprofloxacin 0.3% group. 4-6 drops of ciprofloxacin 0.3% or Cetraxal Plus were instilled in the affected ear canal TID for 8 days (valid range 7-10 days).

The primary efficacy endpoint was clinical success (clinical and bacteriological cure). Treatment was considered to be successful when there was clinical cure + negative culture, or when there was clinical cure + no available culture result due to lack of otorrhea at EOT. Treatment was considered to be a failure when there was a positive culture and/or a lack of clinical cure.

Results: In the ITT population (294 in ciprofloxacin group and 296 Cetraxal Plus group), clinical success was observed in 82% in ciprofloxacin group and in 89% in Cetraxal Plus group; the difference between treatment groups was 7.2% (90% CI 2.5%, 12.0%) in favour of Cetraxal Plus.

In the study by Pistorius et al (randomised, active-controlled, parallel group, open, multicenter), in total 842 patients aged at least 2 years with acute diffuse OE of less than 3 weeks' duration were enrolled at 30 study centers in the US. Of these 703 were evaluable for efficacy (239 in ciprofloxacin 0.2% ear solution 236 in ciprofloxacin plus hydrocortisone (HC) 1% and 228 in PNH groups). In ciprofloxacin 0.2% and ciprofloxacin plus HC 1% groups, patients received 3 drops BID and in PNH group, 3 drops TID (up to 12 years) or 4 drops TID (patients aged 13 years or older) for 7 days.
Inclusion and exclusion criteria for this study were similar to those for the pivotal study (CIPROT III/03 IA 02) (see above).
Study visits were at baseline, on Day 2 or 3 of treatment, at 3 to 10 days after EOT, and at 14 to 28 days after EOT. Bacterial cultures were taken at baseline and at the 2 post-treatment study visits.

The primary efficacy endpoint was clinical success (resolution plus improvement) at 3 to 10 days after EOT. *The secondary endpoint* was bacteriologic success (eradication plus presumed eradication) in patients from whom a pathogen had been isolated before treatment.
Two-sided 95% CIs were calculated for the difference between treatment groups (ciprofloxacin minus PNH or ciprofloxacin plus HC minus PNH) in proportion of patients achieving each endpoint.
The treatment groups were considered equivalent at the 2.5% level of significance if the lower limit of the 95% CI was -10% or greater. Time to end of pain (TEOP) was determined for each treatment group.

Results: The clinical success was 93% for ciprofloxacin, 90% for ciprofloxacin plus HC, and 87% for PNH in the efficacy-valid population and 91% for ciprofloxacin, 91% for ciprofloxacin plus HC, and 89% for PNH in the ITT population. Based on these results, ciprofloxacin otic solution was determined to be statistically equivalent to the approved comparator, PNH.
Clinical resolution occurred in 76% of patients treated with ciprofloxacin, 71% treated with ciprofloxacin plus HC, and 74% treated with PNH. The incidence of bacteriologic success was 92% for ciprofloxacin, 95% for ciprofloxacin plus HC, and 87% for PNH.
The large majority of isolates were *Pseudomonas aeruginosa*. Bacteriologic success (eradication or presumed eradication at EOT) occurred in 92% in the ciprofloxacin group, 95% in the ciprofloxacin plus HC group, and 87% in the PNH group.
This study briefly described an old study from 1999 to support the efficacy of ciprofloxacin otic solution. The results seem to be supportive. The doses are not entirely equivalent to the claimed dosage in the present application.

Other data
Published Studies (from 1989 to 2004 years) in children and adults with ear disorders, where ciprofloxacin solution at concentrations 0.2%, 0.3%, or 0.5% was applied in the ear canal to support the efficacy of ciprofloxacin otic solutions in OE are provided. Some of these studies were open-label, uncontrolled

studies with a variety of treatments as comparators [e.g tobramycin solution, Auricularum powder (dexamethasone, oxytetracycline, polymyxin B, and nystatin), gentamicin 0.3%]. The methods and endpoints of these studies varied but clinical results in ciprofloxacin groups were remarkable. In general, treatment with topical ciprofloxacin solutions appeared to be at least as effective in the treatment of OE as PNH, which has long been approved for this indication and is commonly used in the US. This data has at most a supportive character.

Overall conclusion on efficacy

Overall, the pivotal study CIPROT III/03 IA 02 data supported by additional studies published support the claim of the MAH that Cetraxal 2 mg/ml ear drops solution is effective at the recommended dosage in the sought indication in children, adolescents and adults.

The exact indication and contraindications were thoroughly discussed; see below under 'Product information – discussion on SPC'.

Clinical safety

Cetraxal 2 mg/ml ear drops solution which has an acidic pH, is intended for use in patients with uncomplicated OE without tympanic membrane perforations. Tympanic membrane perforation is a potential risk condition for ototoxicity, as the medication could gain access to the middle ear structures if the tympanic membrane is not intact.

The use of Cetraxal 2 mg/ml ear drops solution demonstrated acceptable safety in the provided main studies. All adverse events reported during study CIPROT III/03 IA 02 were mild and transient. Furthermore, Cetraxal 2 mg/ml ear drops solution is intended for use by patients with uncomplicated OE; patients with tympanic membrane perforations were excluded from the provided main clinical studies.

In total few cases of adverse reactions were reported in the ciprofloxacin group {in 92 patients (28.8%)} in the pivotal study. The most frequently observed adverse events were transient and not clinically significant. The same holds for paediatric patients (children from 2 years and older). Although no data is available on patients less than 2 years old (only Quesada et al., 1999. *Results for the paediatric subpopulation presented in* Quesada et al., 1998, but the data is scarce) there are no specific safety concerns in the paediatric population wich would preclude use of this product in patients one year and older.

Risk management plan

Ciprofloxacin was first approved in 1987, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ciprofloxacin can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

Discussion on SPC

In accordance with the RMS' and CMS' comments, the MAH eventually agreed to adjust the indication to reflect that Cetraxal 2 mg/ml is intended for the treatment of acute otitis externa in patients with *an intact tympanic membrane.*

There is no experience to support the use of Cetraxal 2 mg/ml in patients with tympanic membrane perforation and the safety has not been established. Moreover, eardrum perforation was an exclusion criterion for the pivotal study submitted by the MAH.

A discussion was held whether a contraindication should be included for tympanic membrane perforation.

No human data or strong nonclinical data are available and given the available animal data suggestive of no ototoxicity, a precautionary statement for patients with known, suspected or at risk of perforation is justified. The contraindication *tympanic membrane perforation* was not included and a precautionary

statement was added; in addition to the restricted wording of the indication, a cross-reference to section 4.4 was added in section 4.1 to draw attention to this precaution.

In accordance with further comments from the member states, section 5.3 was adapted to reflect the available data in animals and as concluded in the EU Worksharing procedure on paediatric data for Ciloxan eye- and eardrops.

One of the member states also proposed including use by children up to 1 year as a contraindication. This information is sufficiently reflected in section 4.4 as an additional statement was included in section 4.4 in line with the EU Worksharing procedure on paediatric data for Ciloxan eye- and eardrops.

Section 5.1 was adapted in line with the CHMP article 30 referral article concerning ciprofloxacin via systemic routes of administration (European Commission decision: 7.10.2008) and in line with the final wording of the Ciproxina renewal for the same indication.

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questionnaire consisted of 12 specific and 3 general questions. The questions proved to be effective and reliable during the pilot test and it was used during both the first and the second test rounds.

During the first test round with ten participants, 97.5% of the requested information in the PIL was found and understood. During the second round with another 10 participants, 98.3% of the requested information was found and understood. With these scores, the formal success criteria are met.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The member states, on the basis of the data submitted, considered that Cetraxal 2 mg/ml ear drops, solution demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

Cetraxal 2 mg/ml ear drops has a proven chemical-pharmaceutical quality.

Non-clinical aspects of ciprofloxacin were sufficiently reviewed and discussed based on literature. To support the application, some additional studies were performed in relation to the route of administration: a study on repeat dose toxicity after topical administration, and two local toxicity studies.

Sufficient data were obtained from the pivotal study CIPROT III/03 IA 02. These data supported by additional published studies are in favour of the claim of the MAH that Cetraxal 2 mg/ml ear drops solution is effective at the recommended dosage in the sought indication in children, adolescents and adults. Furthermore, the state of the art based on the clinical experience in the indication approved in the Netherlands for Ciprofloxacine FDC 3 mg/ml, ear drops can be considered supportive, because a similar dosage was used in the pivotal study with Cetraxal 2 mg/ml ear drops. The product demonstrated acceptable safety in the provided main studies.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The product information for Cetraxal has been adequately adapted in accordance with the member states' comments.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that Cetraxal 2 mg/ml ear drops, solution demonstrated sufficient evidence of efficacy and safety, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 December 2010. Cetraxal 2 mg/ml ear drops, solution is authorised in the Netherlands on 6 January 2011.

A European harmonised birth date has been allocated (31 January 1987) and subsequently the first data lock point for ciprofloxacin is January 2013. The first PSUR will cover the period from December 2010 to January 2013, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: December 2015.

The following post-approval commitment has been made during the procedure:

<u>Quality - medicinal product</u>

- The MAH committed to provide stability data to fully support the claimed shelf-life of 24 months.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CITT	Clinical Intent-to-treat
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CNS	Central Nervous System
CPP	Clinical Per-Protocol
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EOT	End of Treatment
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MITT	Microbiological Intent-to-treat
MPP	Microbiological Per-Protocol
OE	Otitis Externa
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PNH	Polymyxin B sulfates, Neomycin and Hydrocortisone
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TOC	Test-of-Cure
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached