CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-537

MEDICAL REVIEW(S)

Medical Officer's Review of NDA
NDA 21-537
Ciprofloxacin 0.3% and Dexamethasone 0.1% Otic Suspension

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Executive Summary

1. Recommendations

1.1. Acute Otitis Externa

The applicant has submitted two studies demonstrating that Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) otic suspension is noninferior to the approved comparator Cortisporin (neomycin 0.35%, polymyxin B 10,000 IU/mL, hydrocortisone 1.0%) otic suspension for the treatment of acute otitis externa (AOE) in pediatric and adult patients. The applicant did not demonstrate the superiority of the combination over a topical ciprofloxacin preparation alone, however. In the AOE studies, the most frequently reported Ciprodex-related adverse event was ear pruritis (1.5%). No serious adverse events were reported in Ciprodex patients in these studies.

Ciprodex is at least as effective as the Cortisporin antibiotic-steroid combination for AOE, and it was demonstrated to be effective in acute otitis media in patients with tympanostomy tubes (AOMT). From a clinical perspective, Ciprodex may be approved for the treatment of AOE due to *Pseudomonas aeruginosa* and *Staphylococcus aureus* in pediatric (age 6 months and older), adult, and elderly patients.

1.2. Acute Otitis Media in Patients with Tympanostomy Tubes

The applicant has submitted two studies demonstrating that Ciprodex is effective for the treatment of AOMT. The first study showed that the combination product was superior to a topical ciprofloxacin preparation alone for a clinically significant endpoint, time to cessation of otorrhea. The second study showed noninferiority to the approved comparator ofloxacin 0.3% otic solution. In the AOMT studies, the most frequently reported Ciprodex-related adverse events were ear discomfort (stinging, burning; 3.0%) and ear pain (2.3%). No serious treatment-related adverse events were reported in Ciprodex patients.

From a clinical perspective, these studies support approval of Ciprodex for the treatment of AOMT due to *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *P. aeruginosa* in pediatric patients 6 months to 12 years of age.

2. Summary of Clinical Findings

2.1. Brief Overview of Clinical Program

Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) otic suspension is a topical fluoroquinolone and corticosteroid combination with the following proposed treatment indications:

- acute otitis externa in pediatric (age 6 months and older), adult, and elderly patients, and
- acute otitis media [redacted] ympanostomy tubes in patients age 6 months and older.

This submission contains data from three phase 1 studies: a skin sensitization study (C-97-56) which enrolled 574 healthy adults, and two pharmacokinetic studies in patients undergoing tympanostomy tube insertion (C-00-68 and C-02-58). C-02-58 was performed to obtain additional data to supplement the valid data from C-00-68; 11 patients received Ciprodex in the combined studies. The applicant performed two clinical studies (C-98-18 and C-98-19) with enrollment of 1377 patients to support the AOE indication and two clinical studies (C-99-59 and C-00-52) with enrollment of 800 patients to support the AOMT indication. The numbers of volunteers or patients exposed to Ciprodex were 231 in the skin sensitization study, 11 in the pharmacokinetic studies, and 937 in the phase 2 and 3 studies (AOE, 537; AOMT, 400).

2.2. Efficacy

2.2.1. Acute Otitis Externa

Protocol C-98-18 was a three-arm trial comparing Ciprodex with a 0.3% topical ciprofloxacin preparation alone and with Cortisporin for the treatment of AOE. This trial was intended to demonstrate superiority of the combination product to ciprofloxacin alone in time to end of pain and noninferiority of Ciprodex to each of the comparators in clinical response at the test of cure visit. This trial enrolled 909 pediatric and adult patients, 785 of whom were clinically evaluable in a revised per protocol analysis which incorporated on-therapy treatment failures. The primary outcome measure for the demonstration of noninferiority was clinical response in the per protocol population at the test of cure visit 10 (±3) days following completion of therapy. In this analysis, cure rates were 86.6% (227/262) for Ciprodex, 85.8% (235/274) for ciprofloxacin alone, and 83.5% (208/249) for Cortisporin. The difference in response rate for Ciprodex vs. ciprofloxacin alone was 0.9% (95% confidence interval (CI), -5.0% to 6.7%) and for Ciprodex vs. Cortisporin was 3.1% (95% CI, -3.1% to 9.3%); each comparison demonstrated noninferiority of Ciprodex. Analyses of several microbiologically evaluable patient subsets and of the intent to treat (ITT) population were consistent with the primary analysis. The primary outcome measure for the demonstration of superiority was time to end of pain in the ITT population. The median time to cessation of ear pain in both the Ciprodex and ciprofloxacin groups was 5 days in each of the applicant's analysis populations. The applicant failed to demonstrate a significant clinical benefit of the combination product compared with ciprofloxacin alone.

Protocol C-98-19 compared Ciprodex with Cortisporin and was intended to demonstrate noninferiority of Ciprodex in clinical and microbiologic responses at the test of cure visit. This trial enrolled 468 pediatric and adult patients, 410 of whom were clinically evaluable in the revised per protocol analysis. The primary outcome measure for clinical efficacy was clinical response in the per protocol population at the test of cure visit 10

(±3) days following completion of therapy. In this analysis, cure rates were 93.6% (189/202) for Ciprodex and 88.9% (185/208) for Cortisporin. The difference in response rate was 4.6% (95% CI, -1.3% to 10.6%). The primary outcome measure for microbiologic efficacy was pathogen eradication in the per protocol population at the test of cure visit. Analyses of various microbiologically evaluable subsets demonstrated success rates of 91.9% to 94.5% for Ciprodex and 85.4% to 86.9% for Cortisporin. For each subset, success rates were approximately 6% to 8% greater for Ciprodex. The clinical and microbiologic efficacy analyses demonstrate the noninferiority of Ciprodex to Cortisporin.

These studies demonstrate that Ciprodex is noninferior to the approved comparator Cortisporin for the treatment of AOE. Protocol C-98-18 did not demonstrate the superiority of the combination over ciprofloxacin alone, however.

The question of optimal therapy for AOE, including the need for anti-inflammatory activity, is complicated. The efficacy of Cortisporin or of its components for the treatment of AOE, while generally accepted, is not well-established. This application may be approved on the basis of the demonstration that Ciprodex is at least as effective as the Cortisporin antibiotic-steroid combination, as well as the demonstration of efficacy of Ciprodex in AOMT. The microbiologic data submitted support approval of Ciprodex for the treatment of AOE due to *P. aeruginosa* and *S. aureus*.

2.2.2. Acute Otitis Media in Patients with Tympanostomy Tubes

Protocol C-99-59 compared Ciprodex with a 0.3% topical ciprofloxacin preparation alone for the treatment of AOMT and was intended to demonstrate superiority of the combination product in time to cessation of otorrhea. This trial enrolled 201 pediatric patients, 198 of whom were included in the ITT analysis. The median time to cessation of otorrhea in the Ciprodex group was 4 days and in the ciprofloxacin group was 5 days. This finding was consistent for each of the applicant's analysis populations (ITT, per protocol, and modified ITT and per protocol), with *p*-values for the differences in median duration ranging from 0.0002 to 0.0047 (survival analysis using log-rank test). This 1-day difference in median time to cessation of otorrhea is statistically and clinically significant. For the secondary clinical and microbiologic efficacy endpoints at the test of cure visit, Ciprodex was noninferior to ciprofloxacin alone. This trial was not designed to demonstrate superiority for these endpoints.

Protocol C-00-52 compared Ciprodex with ofloxacin and was intended to demonstrate noninferiority of Ciprodex in clinical and microbiologic responses at the test of cure visit. This trial enrolled 599 pediatric patients, 456 of whom were clinically evaluable in the revised per protocol analysis. The primary outcome measure for clinical efficacy was clinical response in the per protocol population at the test of cure visit 17 (+3) days following study entry. In this analysis, cure rates were 85.6% (202/236) for Ciprodex and 79.1% (174/220) for ofloxacin. The difference in response rate was 6.5% (95% CI, -0.5% to 13.5%). The primary outcome measure for microbiologic efficacy was pathogen eradication in the per protocol population at the test of cure visit. Analyses of

various microbiologically evaluable subsets demonstrated success rates of 88.1% to 91.2% for Ciprodex and 80.7% to 81.8% for ofloxacin. For each subset, success rates were approximately 7% to 10% greater for Ciprodex. The clinical and microbiologic efficacy analyses demonstrate the noninferiority of Ciprodex to ofloxacin.

These studies demonstrate that Ciprodex is effective for the treatment of AOMT. Protocol C-99-59 showed that the combination product was superior to ciprofloxacin alone for a clinically significant endpoint, time to cessation of otorrhea. Protocol C-00-52 showed noninferiority to the approved comparator ofloxacin. The microbiologic data submitted support approval of Ciprodex for the treatment of AOMT due to *S. aureus*, *S. pneumoniae*, *H. influenzae*, *P. aeruginosa*, and *M. catarrhalis*.

2.3. Safety

2.3.1. Phase 1 Studies

In the skin sensitization study, 231 healthy adults were exposed to Ciprodex. The most frequently reported adverse events were headache (10.4%), rhinitis (5.2%), pain (3.0%), dyspepsia (2.6%), and dysmenorrhea (2.6%). No adverse events were considered by investigators to be treatment-related.

In the pharmacokinetic studies, 11 pediatric patients were exposed to Ciprodex following tympanostomy tube placement. The most frequently reported adverse event was pain, which was reported in 3 patients (27%). No adverse events were considered by the investigator to be treatment-related.

2.3.2. Phase 2 and 3 Studies

In the AOE studies, 537 adult and pediatric patients received Ciprodex. The most frequently reported adverse events in these patients were headache (8.4%), rhinitis (4.6%), otitis media (3.7%), otitis externa in the nonstudy ear (3.5%), increased cough (2.4%), pharyngitis (2.4%), nonotic pain (2.2%), and ear pruritis (2.0%). These events were generally considered to be mild to moderate in intensity. Most of these adverse events are symptoms or manifestations of the underlying disease process or a concurrent illness and are not related to study drug administration. The most frequently reported treatment-related adverse event in Ciprodex patients was ear pruritis (1.5%). Other treatment-related adverse events included ear debris (0.6%), superimposed ear infection (0.6%), ear congestion (0.4%), ear pain (0.4%), erythema (0.4%), and single reports of ear discomfort, decreased hearing, and ear disorder (tingling). All of the treatment-related adverse events were considered to be mild to moderate in intensity. Two Ciprodex patients were discontinued because of treatment-related adverse events; both developed fungal superinfections. No serious adverse events were reported in Ciprodex patients in these studies.

In the AOMT studies, 400 pediatric patients received Ciprodex. The most frequently reported adverse events in these patients were fever (8.5%), otitis media in the nonstudy

ear (7.3%), rhinitis (6.3%), ear pain (5.5%), infection (primarily upper respiratory, 4.5%), ear discomfort (3.0%), increased cough (3.0%), nonotic pain (2.5%), vomiting (2.3%), and ear discharge (2.0%). These events were generally considered by investigators to be nonserious and mild to moderate in intensity. Most of these adverse events are symptoms or manifestations of the underlying disease process or a concurrent illness and are not related to study drug administration. The most frequently reported treatment-related adverse events in Ciprodex patients were ear discomfort (burning, stinging; 3.0%) and ear pain (2.3%). Other treatment-related adverse events included ear precipitate (residue, 0.5%), irritability (0.5%), taste perversion (0.5%), and single reports of tympanostomy tube blockage, ear pruritis, oral moniliasis, crying, dizziness, and erythema. All of the treatment-related adverse events were considered to be mild to moderate in intensity. One Ciprodex patient was discontinued because of treatment-related ear discomfort (burning). One Ciprodex patient had a serious adverse event (abdominal pain) that was determined to be unrelated to study therapy. No serious treatment-related adverse events were reported in Ciprodex patients in these studies.

Ciprodex is safe and well-tolerated in the treatment of AOE and AOMT. The reported Ciprodex-related adverse events are similar in incidence and type to those reported with the approved comparator drugs in these studies. They are also similar in incidence and type to the adverse events listed in the package inserts of these and other recently-approved topical otic antimicrobials. The proposed labeling lists adverse reactions by indication and includes all of the treatment-related adverse events reported in study patients who received Ciprodex.

2.4. Dosing

The proposed dosage for all patients with AOE or AOMT is 4 drops (0.14 mL; 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for 7 days. This dosage is effective and safe.

2.5. Special Populations

In the AOE studies, cure rates were approximately 6% to 12% greater for pediatric patients compared with adults. Few elderly patients were enrolled; cure rates were similar to those for other adults. Adverse events were reported more commonly in adults than in children. Elderly patients had fewer adverse events than other adults. There were no significant differences in efficacy or safety within age groups across drug treatments.

The AOMT studies were performed only in pediatric patients. Cure rates were approximately 7% to 10% lower for infants and toddlers than for older children. Adverse events were reported more commonly in infants and toddlers than in older children. Across drug treatments, subgroup analyses by age were similar to the overall efficacy and safety analyses.

For each indication, there were no significant differences in the efficacy or safety of each study drug when data were analyzed by gender or race (white, black, other). Across drug

treatment; subgroup analyses by gender or race were similar to the overall efficacy and safety analyses.

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA
NDA 21-537

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Contact: Seane D. Jones, Assistant Director, Regulatory Affairs

Date of Submission: 9/25/02

Date Review Completed: 7/17/03

1. Introduction and Background

1.1. Drug Identification

1.1.1. Generic Name: Ciprofloxacin HCl 0.3% and dexamethasone 0.1% otic suspension

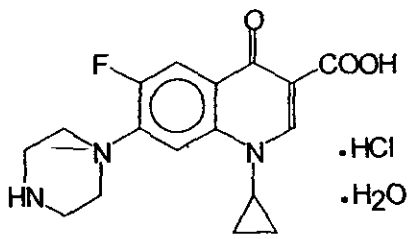
1.1.2. Trade Name: CIPRODEX® Otic Suspension

1.1.3. Chemical Names:

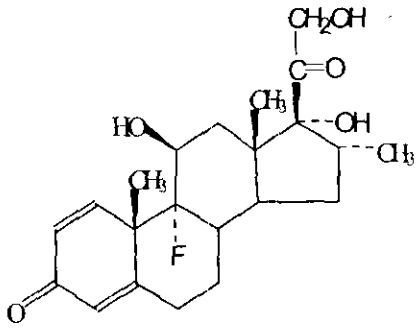
Ciprofloxacin HCl: 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate

Dexamethasone: 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione

1.1.4. Chemical Structures:



Ciprofloxacin HCl



Dexamethasone

1.1.5. Molecular Formulas and Weights

Ciprofloxacin HCl: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$; 385.82

Dexamethasone: $C_{22}H_{29}FO_5$; 392.47

1.1.6. Drug Class: Topical fluoroquinolone and corticosteroid combination

1.1.7. Proposed Indications

The proposed indications for ciprofloxacin and dexamethasone otic suspension are for the treatment of:

- acute otitis externa in pediatric (age 6 months and older), adult, and elderly patients, and
- acute otitis media tympanostomy tubes in patients age 6 months and older.

The recommended dosage regimen for all patients is 4 drops (0.14 mL; 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for 7 days.

1.2. State of Armamentarium for Indications

1.2.1. Acute Otitis Externa

Products available for the treatment of acute otitis externa (AOE) include:

- Ciprofloxacin HCl 0.2% and hydrocortisone 1% otic suspension (CIPRO HC® OTIC)
- Ofloxacin 0.3% otic solution (FLOXIN® OTIC)
- Antibiotic-steroid suspensions and solutions containing polymyxin B or colistin, neomycin, and hydrocortisone (Cortisporin® and others)
- Miscellaneous otic preparations containing ingredients such as acetic acid, boric acid, or chloroxylenol, with or without hydrocortisone

In addition, dexamethasone 0.1% ophthalmic solution is approved for the treatment of "selected purulent and nonpurulent infective otitis externa when the hazard of steroid use is accepted to obtain an advisable diminution in edema and inflammation" (Decadron® Phosphate Ophthalmic Solution label). Ophthalmic aminoglycosides and fluoroquinolones are also prescribed off-label for AOE.

1.2.2. Acute Otitis Media in Patients with Tympanostomy Tubes

The only product approved for the treatment of acute otitis media in patients with tympanostomy tubes (AOMT) is ofloxacin otic solution, which is also approved for the treatment of chronic suppurative otitis media (CSOM) and AOE. Other prescribed treatments include off-label use of drugs approved for AOE; ophthalmic aminoglycosides

and fluoroquinolones, often combined with oral antimicrobial therapy; oral antimicrobial therapy alone; or, in severe or refractory cases of AOMT, intravenous antimicrobial therapy with an antipseudomonal agent.

1.3. Important Milestones in Product Development

November 26, 1997: IND 54,670 was submitted by Alcon for the proposed indication of AOE. The package contained protocols for a skin sensitization study (C-97-56) and two efficacy trials (C-97-48 and C-97-50). C-97-48 was a three-arm trial comparing Ciprodex with ciprofloxacin (CILOXAN®) alone and Cortisporin, and was intended in part to demonstrate superiority of the combination product to ciprofloxacin alone in time to end of pain. C-97-50 was a noninferiority trial comparing Ciprodex with Cortisporin.

November 15, 1999: Alcon submitted an IND amendment containing a development plan for the AOMT indication proposing two phase 1 pharmacokinetic studies, a phase 2 trial, and two phase 3 trials. The clinical protocol for the proposed phase 2 study (C-99-59) comparing Ciprodex with ciprofloxacin alone was submitted.

November 20, 2000: Alcon submitted a clinical protocol for a second AOMT trial (C-00-52) comparing Ciprodex with ofloxacin (FLOXIN® OTIC).

March 28, 2001: Alcon submitted a new pharmacokinetic protocol for the AOMT indication (C-00-68), citing an inability to obtain institutional review board approval for one of the original proposed studies and the refusal of patients to enroll in the second study.

February 13, 2002: At the pre-NDA meeting, Alcon proposed to file for approval of the AOMT indication based on findings of superiority to ciprofloxacin alone in C-99-59 and of noninferiority to ofloxacin in C-00-52. The division stated that "the clearest win is when the study drug shows superiority but without that it is important to show that use of Ciprodex provides an advantage to use of ciprofloxacin alone." Alcon also asked whether their plan to file for the AOE indication was acceptable, given the effect of the steroid component in the AOMT studies. The division stated that this was a review issue and that the data needed to show a "clear advantage of the combination over plain ciprofloxacin."

June 13, 2002: Alcon submitted correspondence from [redacted] concerning an investigation into misconduct by [redacted] M.D., one of two investigators for the pharmacokinetic study, C-00-68. The division requested an investigation by CDER's Division of Scientific Investigations (DSI).

September 25, 2002: Alcon submitted NDA 21-537.

November 6, 2002: The division informed Alcon of the likely need for additional subjects in C-00-68 because of uncertainty that data obtained at the [redacted] site could be accepted to support the NDA.

January 9, 2003: DSI requested a for cause inspection of the site by the Investigations Branch, Office.

January 16, 2003: Alcon submitted a new pharmacokinetic protocol (C-02-58). The division agreed that data from patients in C-02-58 could be combined with data from patients in C-00-68 who were not enrolled at the site.

January 21, 2003: Alcon submitted the four-month safety update.

March 21, 2003: DSI issued a report recommending that all data from the site not be used in support of NDA 21-537

March 28, 2003: Alcon submitted a pharmacokinetics technical report combining valid data from subjects in C-00-68 with new subjects from C-02-58.

1.4. Other Relevant Information

Ciprofloxacin and dexamethasone otic suspension is not approved in any other countries.

1.5. Pharmacologically Related Agents

Ciprofloxacin

- Ciprofloxacin HCl 0.2% and hydrocortisone 1% otic suspension (CIPRO HC® OTIC, NDA 20-805), indicated for the treatment of AOE due to susceptible strains of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Proteus mirabilis*

- Ciprofloxacin HCl 0.3% ophthalmic solution (CILOXAN®), indicated for the treatment of corneal ulcers caused by susceptible strains of *P. aeruginosa*, *Serratia marcescens*, *S. aureus*, *Streptococcus pneumoniae*, and viridans group streptococci; and for the treatment of bacterial conjunctivitis caused by susceptible strains of *Haemophilus influenzae*, *S. aureus*, and *S. pneumoniae*

- Ciprofloxacin HCl 0.3% ophthalmic ointment (CILOXAN®), indicated for the treatment of bacterial conjunctivitis caused by susceptible strains of *S. aureus*, *Staphylococcus epidermidis*, *S. pneumoniae*, viridans group streptococci, and *H. influenzae*

- Ciprofloxacin tablets and oral suspension (CIPRO®), indicated for the treatment of urinary tract infections, acute uncomplicated cystitis in females, chronic bacterial prostatitis, lower respiratory tract infections, acute sinusitis, skin and skin structure infections, bone and joint infections, complicated intraabdominal infections, infectious diarrhea, typhoid fever, uncomplicated cervical and urethral gonorrhea, and post-exposure inhalational anthrax

- Ciprofloxacin for intravenous infusion (CIPRO® I.V.), indicated for the treatment of urinary tract infections, lower respiratory infections, nosocomial pneumonia, skin and skin structure infections, bone and joint infections, complicated intraabdominal infections, acute sinusitis, chronic bacterial prostatitis, empiric therapy for febrile neutropenic patients (in combination with piperacillin sodium), and post-exposure inhalational anthrax

Dexamethasone

- Dexamethasone phosphate 0.1% ophthalmic solution, indicated for steroid responsive inflammatory conditions of the eye and of the external auditory meatus
- Dexamethasone phosphate 0.05% ophthalmic ointment, indicated for steroid responsive inflammatory conditions of the eye
- Other formulations of dexamethasone include topical cream, aerosol spray, elixir, tablets, and several injectable preparations.

Investigational Otic

- [redacted]
- [redacted]

Other Topical Fluoroquinolones

- Norfloxacin 0.3% ophthalmic solution
- Ofloxacin 0.3% ophthalmic solution
- Levofloxacin 0.5% ophthalmic solution
- Moxifloxacin HCl 0.5% ophthalmic solution

2. Clinically Relevant Findings from Other Disciplines

2.1. Chemistry

Milton Sloan, Ph.D., was the chemistry reviewer for this NDA. Dr. Sloan recommended approval this application from the chemistry, manufacturing, and control perspective. Please refer to his review for further details.

2.2. Pharmacology and Toxicology

Amy Ellis, Ph.D., was the pharmacology and toxicology reviewer for this NDA. Dr. Ellis reported that Ciprodex did not induce dermal sensitization in guinea pigs. One study in guinea pigs of intratympanic administration of Ciprodex twice daily for 28 days showed middle ear irritation consistent with that seen with other compounds but no other evidence of ototoxicity. A second study in guinea pigs in which Ciprodex (with or without degradation products) was administered intratympanically twice daily for 14 days reported evidence of outer hair cell loss from the basal region of the cochlea in 2 of 10 animals in each Ciprodex group. Dr. Ellis concluded, based on review of all of the data, that Ciprodex is unlikely to be ototoxic. Please refer to her review for further details.

2.3. Microbiology

Please refer to the microbiology review by Harold Silver.

2.4. Statistics

Please refer to the statistical review by Joel Jiang, Ph.D.

3. Human Pharmacokinetics and Pharmacodynamics

Paul Buehler, Pharm.D., Ph.D., was the clinical pharmacology reviewer for this NDA. Dr. Buehler's conclusions include the following; please refer to his review for further details:

Absorption of ciprofloxacin was observed in 9 of 11 pediatric patients who were administered a single 8-drop topical otic dose of Ciprodex (4 drops bilaterally; total dose 0.28 mL; 0.84 mg ciprofloxacin, 0.28 mg dexamethasone) following tympanostomy tube placement. The mean (± S.D.) peak plasma concentration of ciprofloxacin was 1.39 ± 0.88 ng/mL (range [redacted]); 2 of these 9 patients had measurable plasma concentrations 6 hours following administration. Peak plasma concentrations of ciprofloxacin following this dose were approximately 0.1% of peak plasma concentrations following a 250 mg tablet oral dose.

Absorption of dexamethasone was observed in 9 of 10 pediatric patients who were administered a single 8-drop topical otic dose of Ciprodex following tympanostomy tube insertion. The mean (± S.D.) peak plasma concentration of dexamethasone was 1.14 ± 1.54 ng/mL (range [redacted]); 5 of these 9 patients had measurable plasma concentrations 6 hours following administration. Peak plasma concentrations of dexamethasone following this dose were approximately 14% of peak plasma concentrations following a 0.5 mg tablet oral dose. The observed concentrations of dexamethasone are not expected to suppress the hypothalamo-pituitary-adrenal axis.

4. Description of Clinical Data and Sources

This submission contains data from three phase 1 studies: a skin sensitization study (C-97-56) and two pharmacokinetic studies in patients undergoing tympanostomy tube insertion (C-00-68 and C-02-58); C-02-58 was performed to obtain additional data to supplement the valid data from C-00-68. The applicant performed two clinical studies to support the AOE indication (C-98-18 and C-98-19) and two clinical studies to support the AOMT indication (C-99-59 and C-00-52). Table 1 summarizes the submitted trials.

Table 1. Listing of Clinical Trials

Study Number	Population	Test Drugs	Enrollment
Skin sensitization			
C-97-56	Healthy adults	Ciprodex, ciprofloxacin, dexamethasone, or saline, applied as 0.2 mL topical dermal patch: induction 21 days, rest 10-17 days, challenge 2 days	231 Ciprodex 114 Ciprofloxacin 114 Dexamethasone 115 Saline 574 Total
Pharmacokinetics			
C-00-68	Patients 6 months to 21 years undergoing tympanostomy tube placement	Ciprodex, single dose Ciprofloxacin, single dose	5 Ciprodex*
C-02-58	Same as C-00-68	Ciprodex, single dose	6 Ciprodex
Acute otitis externa			
C-98-18	Pediatric patients 1 year and older; adults	Ciprodex, 3 drops (ped) or 4 drops (adult) bid x 7 days; Ciprofloxacin, 3 drops (ped) or 4 drops (adult) bid x 7 days; Cortisporin, 3 drops (ped) or 4 drops (adult) tid x 7 days	305 Ciprodex 305 Ciprofloxacin 299 Cortisporin 909 Total
C-98-19	Pediatric patients 1 year and older; adults	Ciprodex, 3 drops (ped) or 4 drops (adult) bid x 7 days; Cortisporin, 3 drops (ped) or 4 drops (adult) tid x 7 days	232 Ciprodex 236 Cortisporin 468 Total
Acute otitis media in patients with tympanostomy tubes			
C-99-59	Pediatric patients 6 months and older	Ciprodex, 3 drops bid x 7 days; Ciprofloxacin, 3 drops bid x 7 days	103 Ciprodex 98 Ciprofloxacin 201 Total
C-00-52	Pediatric patients 6 months and older	Ciprodex, 4 drops bid x 7 days; Ofloxacin, 5 drops bid x 10 days	297 Ciprodex 302 Ofloxacin 599 Total
*Data from 5 Ciprodex recipients were valid for combined analysis with C-02-58			

Adapted from Overview of Efficacy, Vol. 5, Module 2, Table 2.5.4.3-1 and Synopsis of Individual Studies, Vol. 9, Module 2, Table 2.7.6-1

5. Clinical Review Methods

5.1. Approach to Review

Detailed reviews of the efficacy and safety data are presented by indication for each of the phase 2 and 3 studies. Results of the phase 1 skin sensitization study are presented briefly in section 7.2.4.1 of the integrated summary of safety. The phase 1 pharmacokinetic studies were reviewed in detail by Paul Buehler, Ph.D., Pharm.D. His findings are summarized in section 3 above. Safety data from the phase 1 studies are presented in the integrated summary of safety.

5.2. Materials Consulted

NDA 21-537 was submitted in paper in Common Technical Document format. The applicant provided CD-ROM copies of the application as review aids. Datasets and case report forms (CRFs) were submitted electronically. Additional materials consulted include the IND for this product (IND 54,670), the NDAs for ciprofloxacin and hydrocortisone otic suspension (NDA 20-805) and ofloxacin otic solution (NDA 20-799), and literature references (cited separately).

5.3. Evaluation of Data Quality and Integrity

DSI Audits

DSI performed clinical inspections of two high-enrolling study sites. Jack Anon, M.D., and Rick Fornelli, M.D., of Erie, PA, enrolled 30 patients in C-99-59 and 59 patients in C-00-52. The DSI audit found no deviation from regulations, and the data appeared acceptable. Leslie Kreisler, M.D., of Richmond, VA, enrolled 64 patients in C-00-52. DSI reported that clinical responses for seven patients were changed up to over 1 year after the initial assessment with no explanation provided; for six of the patients, the change was to a more favorable outcome. This medical officer requested Alcon to submit the CRFs of these patients for review. The modified responses were not for test of cure outcomes and were consistent with other clinical data in the CRF and with protocol requirements. In each case, the appropriate test of cure outcome was recorded on the CRF and in the dataset. Dr. Kreisler's data were therefore accepted for this review.

Medical Officer Review of CRFs

This medical officer also performed a blinded review of at least 10% of the CRFs for each of the phase 2 and 3 studies to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with investigators' evaluability and outcome assessments. These evaluations are presented in more detail in the individual study reviews.

Investigator Misconduct in C-00-68

As noted in the above regulatory history, in June, 2002, Alcon submitted correspondence from [redacted] concerning an investigation into misconduct by [redacted], M.D., one of two investigators for the pharmacokinetic study, C-00-68. Dr.

[redacted] was found to have fabricated follow-up data for patients in this study and in a similar study of another investigational otic drug. The division requested an investigation by DSI. On March 21, 2003, DSI issued a report recommending that all data from the [redacted] site not be used in support of NDA 21-537, "because of deliberate and repeated falsification of data, protocol violations, and incomplete and unverifiable records."

In discussions while the investigation was proceeding, the division informed Alcon that the data in question would most likely be considered invalid by the FDA and that data from additional subjects would be needed. In January, 2003, Alcon submitted a new pharmacokinetic protocol (C-02-58) to supplement data from the allowable subjects from C-00-68. The division agreed to accept the new data during the NDA review cycle if they were submitted in time to allow for proper review. On March 28, 2003, Alcon submitted a pharmacokinetics technical report combining valid data from five subjects in C-00-68 with data from six new subjects in C-02-58.

5.4. Ethical Standards

For each of the studies included in this NDA, the applicant stated that institutional review board approval was obtained for each investigator before patient enrollment began, that the study was conducted according to ethical principles originating in the Declaration of Helsinki, and that informed consent was obtained from each patient (or legal representative) before performance of any study procedures.

Comment: As illustrated by the misconduct described above, these assurances do not guarantee the ethical conduct of investigators. The limited DSI audits and CRF sampling by this reviewer did not reveal any additional evidence of misconduct.

5.5. Financial Disclosure

The applicant reported that there were financial arrangements or interests to disclose for 11 investigators in five of the six covered clinical studies. Certification (FDA 3454) and disclosure (FDA 3455) forms were provided for each of these investigators. For each study, the applicant provided an explanation of measures taken to minimize any resultant bias. These measures included investigator masking, randomization, maintenance of unbroken treatment codes, and on-site monitoring. The applicant also stated that there were no financial interests or arrangements with any of the other investigators in these studies.

Comment: This reviewer considers the disclosures to be acceptable.

6. Integrated Review of Efficacy

6.1. Acute Otitis Externa

6.1.1. Conclusions and Critical Differences from Proposed Label Claims

The applicant has submitted two studies demonstrating that Ciprodex is noninferior to the approved comparator Cortisporin for the treatment of AOE. The applicant did not demonstrate the superiority of the combination over ciprofloxacin alone, however. The application may be approved on the basis of the demonstration that Ciprodex is at least as effective as the Cortisporin antibiotic-steroid combination.

The applicant's proposed label claims for the AOE indication follow:

INDICATIONS AND USAGE

CIPRODEX® Otic is indicated for the treatment of infections caused
he designated microorganisms in the specific conditions listed below:

Acute Otitis Externa in pediatric (age 6 months and older), adult and elderly patients due to

Staphylococcus aureus

Pseudomonas aeruginosa

The following is excerpted from the **Clinical Efficacy** section:

6.1.3.1. Protocol C-98-18: "Topical CILODEX (ciprofloxacin 0.3%, dexamethasone 0.1%) Suspension Compared to CILOXAN® (ciprofloxacin 0.3%) Solution and CORTISPORIN® Suspension (neomycin 0.35%, polymyxin 10,000 IU/mL, hydrocortisone 1.0%) for Treatment of Patients with Moderate to Severe Acute Otitis Externa (AOE)"

6.1.3.1.1. Objectives

To evaluate the efficacy and safety of topical CILODEX Suspension; to demonstrate: (i) therapeutic equivalence of CORTISPORIN Suspension and CILODEX based on clinical response at test of cure (TOC) visit (Day 18); (ii) therapeutic equivalence between CILOXAN and CILODEX based on clinical response at the TOC visit; and (iii) superiority of CILODEX relative to CILOXAN Solution with respect to cessation of patient ear pain. (Module 5, Vol. 17, p.572)

Comment: The applicant revised the biostatistics analysis plan (before data were locked) to add a new objective: therapeutic noninferiority of CILOXAN to CORTISPORIN. This was done

6.1.3.1.2. Design: Randomized (1:1:1), observer-blind, comparative, multicenter trial

Comment: A double-blind design was not considered feasible because of differences in dosing regimens and viscosity of study drugs (solution vs. suspension).

6.1.3.1.3. Protocol Overview

6.1.3.1.3.1. Population

6.1.3.1.3.1.1. Inclusion Criteria

Patients enrolled in this study had to be at least 1 year of age with a clinical diagnosis of "moderate" or "severe" AOE, based on a global clinical rating scale (none = 0, mild = 1, moderate = 2, severe = 3). At baseline, each patient had to have a score of 1 or more for edema, 2 or more for overall inflammation (both on a scale 0 to 3 as above), and 2 for tenderness (absent = 1, present = 2).

Comment: The global determination of severity for study entry was based on the overall clinical impression and not on a simple sum of component scores.

6.1.3.1.3.1.2. Exclusion Criteria

Noteworthy exclusion criteria were:

1. Duration of signs or symptoms of AOE for more than 4 weeks

2. Nonintact or perforated tympanic membrane (TM) in the treated ear(s)

3. Clinical diagnosis of chronic suppurative otitis media (CSOM), acute otitis media (AOM), or acute otorrhea in patients with tympanostomy tubes

4. Clinical diagnosis of malignant otitis externa

5. "Overt" fungal AOE

6. "Overt" viral infection of the pinna or TM

7. Congenital abnormalities of the external auditory canal (EAC) or obstructive bony exostoses in the treated ear(s)

8. Mastoid or other suppurative, noninfectious ear disorders (e.g., cholesteatoma) in the treated ear(s)

9. Malignant tumors of the EAC

10. History of otologic surgery. Surgery performed more than 1 year previously and limited to TM was permitted.

11. Seborrheic dermatitis or other dermatologic conditions of the EAC which would complicate evaluation

12. Current or previous use of systemic steroids (within 30 days) or topical otic steroids (within 7 days)

13. Current infection requiring systemic antimicrobial therapy

14. Current use of topical or oral antibiotics; previous use of short-acting (within 3 days) or long-acting (within 7 days) antibiotics

15. Current use of topical or oral antiinflammatory agents

16. Current or previous treatment (within 2 days) with vinegar, alcohol, or other astringents

17. History of an immunosuppressive disorder or receipt of immunosuppressive therapy

18. Diabetes mellitus

Comment: The exclusion criteria are a reasonable attempt to limit the treatment population to patients with AOE and exclude those who might require systemic therapy.

6.1.3.1.3.2. Study Procedures

6.1.3.1.3.2.1. Study Drug Administration

Patients were randomized to receive one of the following study treatments:

- Cilodex, 3 drops (children) or 4 drops (adults) instilled into the affected ear(s) bid for 7 days,
- Ciloxan, 3 drops (children) or 4 drops (adults) instilled into the affected ear(s) bid for 7 days, or
- Cortisporin, 3 drops (children) or 4 drops (adults) instilled into the affected ear(s) tid for 7 days

Comment: The label for Cortisporin states, "treatment should not be continued for longer than 10 days," but does not otherwise specify a recommended duration. FDA recommended the use of 7 days for this trial, the same as when Cortisporin was used as a comparator in the Cipro HC NDA.

For patients who had ear wick insertion, the dose of ototopical therapy was doubled for the first dose only.

6.1.3.1.3.2.2. Study Evaluations

1. Screening Exam
- History
- Clinical assessment
  - AOE severity (4-point scale)
  - Overall ear inflammation (4-point scale)
  - Ear edema (4-point scale)
  - Ear tenderness (present or absent)
  - Otic discharge (present or absent)
- Collection of culture specimen from EAC wall before mechanical cleansing
- Mechanical cleansing of EAC by lavage, dry mop, or suction. if necessary
- Instruction on diary completion
- Dispensation of study drug

Comment: Investigators were instructed to collect a swab specimen from the interior wall of the EAC, avoiding "obvious debris and exudate," before cleansing of the EAC. Collection of the specimen in this manner raises the question of bacterial contamination or overgrowth of exudate and misattribution of pathogenicity to the isolates obtained. The FDA draft guidance on skin and skin structure infections, which is applicable to the AOE indication, recommends that cultures be obtained after debridement of a site.

For patients with bilateral AOE, both ears were treated, and the worse ear was used in analysis. The worse ear was defined as the one with the higher score on assessment of AOE severity at baseline.

2. Visit 2 (Day 3 ± 1)
- Clinical assessment
  - Overall clinical judgment (4-point scale: cured, improved, no change, worse)
  - Overall ear inflammation
  - Ear edema
  - Ear tenderness
  - Otic discharge
- Collection of culture specimen and exit from study if no response to therapy
- Mechanical cleansing as needed
- Review of patient diary

3. Visit 3 (Day 8 ± 1)
- Clinical assessment
- Collection of culture specimen and exit from study if no response to therapy
- Mechanical cleansing as needed
- Review of patient diary
- Collection of remaining study medication

4. Test of Cure Visit (Day 18 ± 3)
- Clinical assessment
- Collection of culture specimen if overall assessment is no change or worse
- Review of patient diary

6.1.3.1.3. Evaluability Criteria

The following evaluability criteria are taken directly from the final version of the study protocol (Module 5, Vol. 17, p.584):

> All patients who receive treatment will be evaluable for Safety and Intent to Treat analysis.
>
> For a patient to be included in the Per Protocol efficacy analysis they must have: (1) a clinical diagnosis of acute otitis externa (AOE) at baseline; (2) met inclusion criteria; (3) received BID (or TID) drug therapy for 80% to 120% of the total recommended dosage; (4) completed a test of cure (TOC) visit within the time window of (10 ± 3) days after the last dose of study medication; and (5) received no other systemic or ototopical antimicrobial or antiinflammatory drugs during the study period.

Comment: The protocol did not specify that all treatment failures should be carried forward in the per protocol analysis, regardless of whether there was a TOC visit.

Microbiologic procedures were defined in a nonclinical study protocol that was appended to the clinical protocol. The microbiology protocol section entitled "Defined Pathogens in Patients with Otitis Externa" states that expected isolates "include but are not limited to the following:"

Gram-Positive Aerobic Bacteria

Staphylococcus

Gram-Negative Aerobic Bacteria

Pseudomonas

In addition, "Any other microorganisms present in essentially pure culture may also be considered as 'pathogens'." (Module 5, Vol. 17, p.681)

Comment: The list of "defined pathogens" includes many species not generally considered pathogens in AOE. Please see the detailed discussion that follows in the indication summary.

6.1.3.1.3.4. Endpoints

As stated previously, there were three co-primary study objectives:

1. Demonstrate therapeutic equivalence between CILODEX and CORTISPORIN Suspension based on clinical response at the TOC visit.

2. Demonstrate therapeutic equivalence between CILODEX and CILOXAN based on clinical response at the TOC visit.

3. Demonstrate superiority of CILODEX relative to CILOXAN Solution with respect to cessation of patient ear pain.

The following describes the endpoint determinations used to meet these objectives (Module 5, Vol. 17, p.585):

> For objectives 1 and 2, the primary clinical efficacy variable under analysis in this study objective is investigator assessment of improvement as measured on a 4-point scale (cure = 0, worse = 3) at the TOC visit. Analyses will be based on the proportion of patients rated cured (clinical response score of 0) at the TOC visit.
>
> The third study objective is to demonstrate superiority of CILODEX relative to CILOXAN with respect to pain. Ear pain will be defined as ending on the first day on which there is no use of analgesics in the prior 24 hours, the diary pain score is zero and the score remains at zero for all subsequent visits.
>
> *Comment: These endpoints were agreed upon following discussions between the applicant and the division at the time of submission of this protocol. The per protocol population was to be used for noninferiority comparisons, and the ITT population for the demonstration of superiority in time to cessation of pain.*

6.1.3.1.3.5. Statistical Considerations

For the sample size calculations, the applicant assumed that clinical cure rates at TOC would be 90% for Cilodex and Ciloxan and 88% for Cortisporin. For the comparison between Cilodex and Cortisporin (objective 1), at least 180 clinically evaluable patients per group were needed to provide 90% probability that the upper 95% confidence interval (CI) for the difference in proportions was less than 10%. For the comparison between Cilodex and Ciloxan (objective 2), at least 235 clinically evaluable patients per group were needed to demonstrate noninferiority of Cilodex. For demonstration of superiority of the combination product (objective 3), Kaplan-Meier survival curves were constructed to evaluate the difference in median time to cessation of pain. At least 285 clinically evaluable patients per group were needed to provide 80% probability of detecting a 1-day difference in median time to cessation of pain.

> *Comment: The expected cure rates and improvement in time to cessation of pain were obtained from previous trials of Cipro HC.*

6.1.3.1.4. Study Results

6.1.3.1.4.1. Demographics

Nine hundred nine patients were randomized to receive one of the study therapies: 305 to receive Ciprodex, 305 to receive Ciloxan, and 299 to receive Cortisporin. Forty-eight U.S. sites enrolled patients, with no site enrolling more than 5% of the total. Table 2 shows the baseline characteristics of the treated patients.

Table 2. Baseline Patient Characteristics

	Ciprodex (N=305)		Ciloxan (N=305)		Cortisporin (N=299)		Total (N=909)	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
1-23 months	3	(1.0)	2	(0.7)	-	-	5	(0.6)
2-11 years	122	(40.0)	137	(44.9)	126	(42.1)	385	(42.4)
12-17 years	66	(21.6)	54	(17.7)	59	(19.7)	179	(19.7)
18-64 years	106	(34.8)	102	(33.4)	107	(35.8)	315	(34.7)
65-74 years	5	(1.6)	5	(1.6)	5	(1.7)	15	(1.7)
≥75 years	3	(1.0)	5	(1.6)	2	(0.7)	10	(1.1)
Mean (years)	21.1		20.6		21.1		20.9	
Range (years)	1 to 88		1 to 88		2 to 85		1 to 88	
Sex								
Male	144	(47.2)	126	(41.3)	133	(44.5)	403	(44.3)
Female	161	(52.8)	179	(58.7)	166	(55.5)	506	(55.7)
Race								
White	271	(88.9)	259	(84.9)	250	(83.6)	780	(85.8)
Black	13	(4.3)	16	(5.2)	16	(5.4)	45	(5.0)
Asian	3	(0.9)	1	(0.3)	3	(1.0)	7	(0.8)
Other	18	(5.9)	29	(9.5)	30	(10.0)	77	(8.5)
Severity								
Moderate	240	(78.7)	237	(77.7)	236	(78.9)	713	(78.4)
Severe	65	(21.3)	68	(22.3)	63	(21.1)	196	(21.6)

Adapted from C-98-18 study report, Volume 16, Tables 11.2-1,11.2-2, and 14.2-125

Comment: The distribution of baseline characteristics was similar for each of the randomized groups.

6.1.3.1.4.2. Evaluability

The per protocol clinically evaluable population was used for the primary efficacy analyses of noninferiority of Ciprodex versus comparators. Table 3 shows the applicant's determinations of patient evaluability.

Table 3. Applicant's Accounting of Patient Evaluability

	Ciprodex (N=305)		Ciloxan (N=305)		Cortisporin (N=299)	
	n	(%)	n	(%)	n	(%)
Per Protocol Evaluable	238	(78.0)	246	(80.7)	228	(76.3)
Per Protocol Unevaluable	67	(22.0)	59	(19.3)	71	(23.7)
Inclusion criteria	1		1		1	
Exclusion criteria	4		1		4	
Excluded concomitant medication	44		43		39	
Protocol violation	1		-		1	
Excluded concomitant disease	1		2		-	
TOC visit outside specified range	2		1		-	
Dosing noncompliance	8		7		9	
Missed visit	6		4		17	

TOC = Test of Cure

Adapted from C-98-18 study report, Volume 16, Table 10.1.2

Comment: This medical officer performed a blinded review of 10% of the case report forms (CRFs) to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with investigators' evaluability and outcome assessments. This reviewer found that the key data transcriptions and outcome assessments were accurate. Review of the CRFs of patients who were deemed unevaluable because of "excluded concomitant medication" revealed that the majority of these cases were actually treatment failures who were discontinued from the study and prescribed alternative therapy, which made them unevaluable. These cases were accurately labeled as treatment failures on the CRFs; there were 24 Ciprodex failures, 28 Ciloxan failures, and 21 Cortisporin failures. The applicant discusses these cases separately in the study report section on primary efficacy analyses. The applicant's approach inflates the apparent clinical efficacy of all study treatments. From the Agency's standpoint, these cases should be included as failures in the per protocol analysis. On 4/4/03, the division asked the applicant to submit corrected analyses which incorporated treatment failures. The revised figures that were submitted have been reviewed and are acceptable. In presenting efficacy data, both the applicant's original and corrected results are shown. Correcting the per protocol population denominators to account for treatment failures provides a more accurate description of drug efficacy.

6.1.3.1.4.3. Efficacy

6.1.3.1.4.3.1. Clinical Efficacy

The primary outcome measure for clinical efficacy was the clinical response in the per protocol population at the TOC visit. Table 4 shows the proportions of patients who were rated as cured in the applicant's original and corrected per protocol analyses, along with pairwise comparisons of treatment differences. Cure rates in the applicant's original per protocol analysis ranged from 91.2% to 95.5%, and in the corrected analysis from 83.5% to 86.6%. For each of the pairwise comparisons, the lower bound of the 95% confidence interval around the treatment difference was greater than -10%.

APPEARS THIS WAY ON ORIGINAL

Table 4. Clinical Outcomes at Test of Cure Visit (Per Protocol)

Per Protocol Analysis						
	Ciprodex		Ciloxan		Cortisporin	
	n/m	(%)	n/m	(%)	n/m	(%)
Original	227/238	(95.4)	235/246	(95.5)	208/228	(91.2)
Corrected	227/262	(86.6)	235/274	(85.8)	208/249	(83.5)

Comparisons				
	Original		Corrected	
	Diff	95% CI	Diff	95% CI
Ciprodex vs. Ciloxan	-0.2	-4.3, 4.0	0.9	-5.0, 6.7
Ciprodex vs. Cortisporin	4.2	-0.8, 9.1	3.1	-3.1, 9.3
Ciloxan vs. Cortisporin	4.3	-0.6, 9.2	2.2	-4.0, 9.2

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions

Adapted from C-98-18 study report, Volume 16, Tables 11.4.1.1-2 and 11.4.1.1-3, and 5/5/03 submission, Table 3a

Comment: The corrected cure rates are approximately 8% to 10% lower than the original rates. Because there were roughly equal numbers of treatment failures in each group, correction of the per protocol denominators in the revised analysis had no significant effect on the pairwise comparisons. In this study, Ciprodex was noninferior to Ciloxan and Cortisporin in clinical response at TOC.

The applicant submitted subgroup analyses by age, sex, and race. Clinical outcomes for each subgroup were similar to those observed in the overall data.

Table 5 shows the proportions of patients who were rated as cured in the applicant's original and corrected ITT analyses, along with pairwise comparisons of treatment differences. Cure rates were similar in all groups in both analyses. For each of the pairwise comparisons, the lower bound of the 95% confidence interval around the treatment difference was greater than -10%.

Table 5. Clinical Outcomes at Test of Cure Visit (ITT)

ITT Analysis						
	Ciprodex		Ciloxan		Cortisporin	
	n/m	(%)	n/m	(%)	n/m	(%)
Original	251/305	(82.3)	250/305	(82.0)	242/299	(80.9)
Corrected	250/305	(82.0)	250/305	(82.0)	239/299	(79.9)

Comparisons				
	Original		Corrected	
	Diff	95% CI	Diff	95% CI
Ciprodex vs. Ciloxan	0.3	-5.8, 6.4	0.0	-6.1, 6.1
Ciprodex vs. Cortisporin	1.4	-4.8, 7.5	2.1	-4.2, 8.3
Ciloxan vs. Cortisporin	1.0	-5.2, 7.2	2.1	-4.2, 8.3

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions

Adapted from C-98-18 study report, Volume 16, Tables 11.4.1.1-2 and 11.4.1.1-3, and 5/5/03 submission, Table 2a

Comment: As expected, the corrected analysis for the ITT population was not significantly different from the original analysis. In the ITT analyses, Ciprodex was noninferior to Ciloxan and Cortisporin in clinical response at TOC.

Microbiologically Evaluable Patients

Comment: The applicant's original analysis considered "defined pathogens" to include a number of organisms of uncertain pathogenicity in AOE. On 4/4/03, the division asked the applicant to perform exploratory analyses on several subsets of microbiologically evaluable patients using the revised per protocol and ITT populations. The requested subsets included: patients with P. aeruginosa or S. aureus; patients with P. aeruginosa, S. aureus, or any other Gram-negative bacteria; patients with any organism in the proposed label; and patients with any organism. The last population is equivalent to the applicant's revised modified per protocol population. The analyses of subsets of isolates submitted in response considered "only the eradicated pre-therapy isolates from patients categorized as 'successes' and the persisting pre-therapy isolates from patients categorized as 'failures'" (5/5/03 response, p.7). Patients with microbiologic outcomes such as superinfection and reinfection were excluded. This reviewer believes that patients with these outcomes should be included in the analyses. The review of ciprofloxacin and hydrocortisone for AOE used this approach. This position is also supported by the draft guidance for uncomplicated and complicated skin and structure infections, which is the most relevant guidance for the AOE indication. In a teleconference on 5/23/03, the applicant agreed to submit lists of patients who had been excluded from isolate level analyses. In the analyses presented in this review (clinical outcomes in microbiologically evaluable patients, microbiologic outcomes, and per pathogen outcomes), the medical officer has modified the tables submitted by the applicant to include all microbiologically evaluable patients in each subset. Patients with microbiologic outcomes other than eradication or presumed eradication are considered to be failures.

Table 6 shows the proportions of patients rated as cured in subsets of microbiologically evaluable patients.

Table 6. Clinical Outcomes in Microbiologically Evaluable Subsets (Per Protocol)

	Ciprodex		Ciloxan		Cortisporin	
Microbiologic Subset	n/m	(%)	n/m	(%)	n/m	(%)
PA/SA	137/159	(86.2)	142/162	(87.7)	123/150	(82.0)
PA/SA/GN	159/181	(87.8)	162/185	(87.6)	142/169	(84.0)
Proposed label	173/199	(86.9)	181/209	(86.6)	159/190	(83.7)
Applicant MPP	198/229	(86.5)	206/236	(87.3)	182/217	(83.9)

n/m = number of cures/number evaluable
PA/SA: *P. aeruginosa* or *S. aureus*
PA/SA/GN: *P. aeruginosa*, *S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 11a, 15a, 19a, and 23a

Comment: Cure rates are similar across subsets for each drug and are similar to the corrected cure rates in the clinically evaluable per protocol population shown in Table 4. For each subset, cure rates for Ciprodex patients are approximately 2% to 4% greater than those for Cortisporin patients.

Time to End of Pain

The final objective of this study was to demonstrate the superiority of the combination product, Ciprodex, to Ciloxan in time to cessation of ear pain. The median time to cessation of ear pain in both the Ciprodex and Ciloxan groups was 5 days. This finding was consistent for each of the applicant's analysis populations (ITT, per protocol, and modified ITT and per protocol). Table 7 shows the results for the ITT analysis.

Table 7. Time to End of Pain (ITT)

	Ciprodex (n=305)	**Ciloxan (n=305)**
Mean (d)	7.14	6.68
Median (d)	5.00	5.00
Standard deviation (d)	5.74	5.27
Range (d)	1 to 21	1 to 21
$p = 0.3369$ for difference in median time to end of pain (log-rank test, Kaplan-Meier survival analysis)		

Adapted from C-98-18 study report, Volume 16, Table 14.2-1

Comment: In this study, the applicant failed to demonstrate a significant clinical benefit of the combination product compared with ciprofloxacin alone.

6.1.3.1.4.3.2. Microbiologic Efficacy

Table 8 shows the proportions of patients with satisfactory microbiologic outcomes in evaluable subsets.

Table 8. Microbiologic Outcomes at Test of Cure Visit (Per Protocol)

	Ciprodex		Ciloxan		Cortisporin	
Microbiologic Subset	n/m	(%)	n/m	(%)	n/m	(%)
PA/SA	139/159	(87.4)	142/162	(87.7)	126/150	(84.0)
PA/SA/GN	161/181	(89.0)	162/185	(87.6)	145/169	(85.8)
Proposed label	175/199	(87.9)	182/209	(87.1)	163/190	(85.8)
Applicant MPP	198/229	(86.5)	205/236	(86.9)	184/217	(84.8)

n/m = number with eradication or presumed eradication/number evaluable
PA/SA: *P. aeruginosa* or *S. aureus*
PA/SA/GN: *P. aeruginosa*, *S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 9a, 13a, 17a, and 21a

Comment: The microbiologic outcome rates are similar across subsets for each drug and correspond closely to the clinical outcome rates. For each subset, eradication and presumed eradication rates for Ciprodex patients are approximately 2% to 4% greater than those for Cortisporin patients.

Pathogen Eradication Rates

Table 9 shows microbiologic response rates for each of the organisms in the applicant's proposed label.

Table 9. Microbiologic Response Rates by Baseline Isolate (Per Protocol)

Baseline Isolate	Ciprodex n/m (%)	Ciloxan n/m (%)	Cortisporin n/m (%)
Gram-positive			
Staphylococcus aureus	17/18 (94)	13/16 (82)	17/17 (100)
Pseudomonas aeruginosa	124/144 (86)	132/150 (88)	117/141 (83)

n/m = number with eradication or presumed eradication/number evaluable
Adapted from 5/5/03 submission, Table 5a

Comment: The response rates for P. aeruginosa and S. aureus in the Ciprodex patients are consistent with the overall microbiologic response rates shown in Table 8. Most of the other organisms in the proposed label occurred infrequently in this study.

6.1.3.1.5. Study Conclusions

In this study, Ciprodex was noninferior to Ciloxan and Cortisporin for the primary endpoint of clinical response at TOC. Microbiologic outcomes support the clinical findings. However, for the final objective of the study, time to cessation of pain, the applicant failed to demonstrate a significant clinical benefit of the combination product compared with ciprofloxacin alone.

6.1.3.2. Protocol C-98-19: "Topical CILODEX (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to CORTISPORIN® Suspension (Neomycin 0.35%, Polymyxin 10,000 IU/mL, Hydrocortisone 1.0%) for Treatment of Patients with Acute Otitis Externa (AOE)"

6.1.3.2.1. Objectives

To evaluate the efficacy and safety of topical CILODEX Suspension; to demonstrate:

1. Therapeutic equivalence of CORTISPORIN Suspension and CILODEX based on clinical response at test of cure (TOC) visit (Day 18);

2. Therapeutic equivalence of CILODEX and CORTISPORIN based on antimicrobial efficacy at the TOC visit. (Module 5, Vol. 12, p.289)

6.1.3.2.2. Design: Randomized (1:1), observer-blind, comparative, multicenter trial

6.1.3.2.3. Protocol Overview

6.1.3.2.3.1. Population

6.1.3.2.3.1.1. Inclusion Criteria

Patients enrolled in this study had to be at least 1 year of age with a clinical diagnosis of "mild," "moderate," or "severe" AOE, based on a global clinical rating scale (none = 0, mild = 1, moderate = 2, severe = 3). At baseline, each patient had to have a score of 1 or more for overall ear inflammation and edema (both on a scale 0 to 3 as above), and 2 for tenderness (absent = 1, present = 2).

Comment: This study differs from C-98-18 by allowing the enrollment of patients with mild AOE. The inclusion of such patients, who may be more likely to have spontaneous resolution, could be a source of bias toward a finding of noninferiority.

6.1.3.2.3.1.2. Exclusion Criteria

The exclusion criteria were the same as in C-98-18 (see section 6.1.3.1.3.1.2., p.21)

6.1.3.2.3.2. Study Procedures

6.1.3.2.3.2.1. Study Drug Administration

Patients were randomized to receive one of the following study treatments:

- Cilodex, 3 drops (children) or 4 drops (adults) instilled into the affected ear(s) bid for 7 days,

- Cortisporin, 3 drops (children) or 4 drops (adults) instilled into the affected ear(s) tid for 7 days

Comment: These dosages are the same as were used in the respective arms of C-98-18.

For patients who had ear wick insertion, the dose of ototopical therapy was doubled for the first dose only.

6.1.3.2.3.2.2. Study Evaluations

Study evaluations were the same as in C-98-18 (see section 6.1.3.1.3.2.2., p.23), except that patient diaries were not kept. There was no time-to-end-of-pain endpoint in this study.

6.1.3.2.3.3. Evaluability Criteria

The evaluability criteria were the same as in C-98-18 (see section 6.1.3.1.3.3., p.24)

> *Comment: As in C-98-18, there was no specification that all treatment failures be carried forward in the per protocol analysis, regardless of whether there was a TOC visit.*

The microbiologic procedures were also the same as in C-98-18, with the identical list of "Defined Pathogens in Patients with Otitis Externa."

6.1.3.2.3.4. Endpoints

The following describes the endpoint determinations used to evaluate the study objectives (Module 5, Vol. 12, p.300):

> The primary clinical efficacy variable under analysis in this study objective is investigator assessment of improvement as measured on a 4-point scale (cure = 0, worse = 3) at the TOC visit. Analyses will be based on the proportion of patients rated cured (clinical response score of 0) at the TOC visit.
>
> *Comment: Assessment of the clinical efficacy objective was the same as in C-98-18.*
>
> The primary microbiological efficacy variable under analysis in this study objective is the eradication of disease-specific pathogens present at enrollment (Day 1) and absent (presumed or documented) at the TOC visit. This analysis utilizes only data from those patients who are micro-evaluable [sic]. Primary analysis will be based on the proportion of patients who demonstrate microbiological eradication at the TOC visit under each of the two treatment regimens.

6.1.3.2.3.5. Statistical Considerations

For the sample size calculations, the applicant assumed that clinical cure rates at TOC would be 90% for Cilodex and 88% for Cortisporin. At least 180 clinically evaluable patients per group were needed to provide 90% probability that the upper 95%

confidence interval (CI) for the difference in proportions was less than 10%. The applicant assumed that microbiological eradication rates at TOC would be 92% for Cilodex and 88% for Cortisporin. At least 160 microbiologically evaluable patients per group were needed to provide 90% probability that the upper 95% CI for the difference in proportions was less than 10%.

6.1.3.2.4. Study Results

6.1.3.2.4.1. Demographics

Four hundred sixty-eight patients were randomized to receive one of the study therapies: 232 to receive Ciprodex and 236 to receive Cortisporin. Twenty-three U.S. sites enrolled patients, with no site enrolling more than 9% of the total. Table 10 shows the baseline characteristics of the treated patients.

Table 10. Baseline Patient Characteristics

	Ciprodex (N=232)		Cortisporin (N=236)		Total (N=468)	
	n	(%)	n	(%)	n	(%)
Age						
1-23 months	-	-	2	(0.8)	2	(0.4)
2-11 years	80	(34.5)	82	(34.7)	162	(34.6)
12-17 years	44	(19.0)	46	(19.5)	90	(19.2)
18-64 years	106	(45.7)	99	(41.9)	205	(43.8)
65-74 years	1	(0.4)	3	(1.3)	4	(0.9)
≥75 years	1	(0.4)	4	(1.7)	5	(1.1)
Mean (years)	22.4		23.2		22.8	
Range (years)	2 to 76		1 to 90		1 to 90	
Sex						
Male	121	(52.2)	116	(49.2)	237	(50.6)
Female	111	(47.8)	120	(50.2)	231	(49.4)
Race						
White	205	(88.4)	204	(86.4)	409	(87.4)
Black	6	(2.6)	8	(3.4)	14	(3.0)
Asian	5	(2.2)	9	(3.8)	14	(3.0)
Other	16	(6.9)	15	(6.4)	31	(6.6)
Severity						
Mild	52	(22.4)	48	(20.3)	100	(21.4)
Moderate	153	(65.9)	152	(64.4)	305	(65.2)
Severe	27	(11.6)	36	(15.3)	63	(13.5)

Adapted from C-98-19 study report, Volume 12, Tables 11.2-2, 11.2-3, and 14.2-42

Comment: The distribution of baseline characteristics was similar for each of the randomized groups.

6.1.3.2.4.2. Evaluability

The per protocol clinically evaluable population was used for the primary clinical efficacy analysis. Table 11 shows the applicant's determinations of patient evaluability.

Table 11. Applicant's Accounting of Patient Evaluability

	Ciprodex (N=232)		Cortisporin (N=236)	
	n	(%)	n	(%)
Per Protocol Evaluable	194	(83.6)	199	(84.3)
Per Protocol Unevaluable	38	(16.4)	37	(15.7)
Inclusion criteria	3		-	
Exclusion criteria	1		1	
Excluded concomitant medication	22		23	
Protocol violation	2		-	
Excluded concomitant disease	2		1	
TOC visit outside specified range	1		3	
Missed visit	7		9	

TOC = Test of Cure

Adapted from C-98-19 study report, Volume 12, Table 10.1-2

Comment: This medical officer performed a blinded review of 13% of the CRFs (approximately 30 CRFs in each treatment group) to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with investigators' evaluability and outcome assessments. This reviewer found that the key data transcriptions and outcome assessments were accurate. Review of the CRFs of patients who were deemed unevaluable because of "excluded concomitant medication" revealed that many of these cases were actually treatment failures who were discontinued from the study and prescribed alternative therapy, which made them unevaluable. These cases were accurately labeled as treatment failures on the CRFs; there were 8 Ciprodex failures and 9 Cortisporin failures. The applicant discusses these cases separately in the study report section on primary efficacy analyses. The applicant's approach inflates the apparent clinical efficacy of all study treatments. From the Agency's standpoint, these cases should be included as failures in the per protocol analysis. On 4/4/03, the division asked the applicant to submit corrected analyses which incorporated treatment failures. The revised figures that were submitted have been reviewed and are acceptable. In presenting efficacy data, both the applicant's original and corrected results are shown. Correcting the per protocol population denominators to account for treatment failures provides a more accurate description of drug efficacy.

6.1.3.2.4.3. Efficacy

6.1.3.2.4.3.1. Clinical Efficacy

The primary outcome measure for clinical efficacy was the clinical response in the per protocol population at the TOC visit. Table 12 shows the proportions of patients who were rated as cured in the applicant's original and corrected per protocol analyses, along with comparisons of treatment differences. Cure rates in the applicant's original per protocol analysis were 93.0% for Cortisporin and 97.4% for Ciprodex, and in the corrected analysis, cure rates were 88.9% and 93.6%, respectively. For each comparison, the lower bound of the 95% confidence interval around the treatment difference was greater than -10%.

Table 12. Clinical Outcomes at Test of Cure Visit (Per Protocol)

Per Protocol Analysis	Ciprodex n/m	(%)	Cortisporin n/m	(%)	Diff	95% CI
Original	189/194	(97.4)	185/199	(93.0)	4.5	-0.2, 9.2
Corrected	189/202	(93.6)	185/208	(88.9)	4.6	-1.3, 10.6

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions
Adapted from C-98-19 study report, Volume 12, Table 11.4.1.1-1, and 5/5/03 submission, Table 3b

Comment: The corrected cure rates are approximately 4% lower than the original rates. Because there were roughly equal numbers of treatment failures in each group, correction of the per protocol denominators in the revised analysis had no significant effect on the comparisons. In this study, Ciprodex was noninferior to Cortisporin in clinical response at TOC.

The applicant submitted subgroup analyses by age, sex, and race. Clinical outcomes for each subgroup were similar to those observed in the overall data.

Table 13 shows the proportion of patients who were rated as cured in the ITT analyses. For this study, no correction of the original ITT analysis was necessary, so only the original analysis is displayed.

Table 13. Clinical Outcomes at Test of Cure Visit (ITT)

ITT Analysis	Ciprodex n/m	(%)	Cortisporin n/m	(%)	Diff	95% CI
Original	206/232	(88.8)	197/236	(83.5)	5.3	-0.9, 11.6

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions
Adapted from C-98-19 study report, Volume 12, Table 11.4.1.1-1

Comment: In the ITT analysis, Ciprodex was noninferior to Cortisporin in clinical response at TOC.

Microbiologically Evaluable Patients

Comment: The approach to the analysis of microbiologically evaluable patients in this study is the same as that used for Protocol C-98-18 (see section 6.1.3.1.4.3.1, p.30). In the analyses that follow (clinical outcomes in microbiologically evaluable patients, microbiologic outcomes, and per pathogen outcomes), the medical officer has modified the tables submitted by the applicant to include all microbiologically evaluable patients in each subset. Patients with microbiologic outcomes other than eradication or presumed eradication are considered to be failures.

Table 14 shows the proportions of patients rated as cured in subsets of microbiologically evaluable patients.

Table 14. Clinical Outcomes in Microbiologically Evaluable Subsets (Per Protocol)

Microbiologic Subset	Ciprodex n/m	Ciprodex (%)	Cortisporin n/m	Cortisporin (%)
PA/SA	118/126	(93.7)	108/123	(87.8)
PA/SA/GN	127/136	(93.4)	125/140	(89.3)
Proposed label	136/145	(93.8)	128/145	(88.3)
Applicant MPP	159/172	(92.4)	152/171	(88.9)

n/m = number of cures/number evaluable
PA/SA: *P. aeruginosa* or *S. aureus*
PA/SA/GNR: *P. aeruginosa*, *S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's modified per protocol population
Adapted from 5/5/03 submission, Tables 11b, 15b, 19b, and 23b

Comment: Cure rates are similar across subsets for each drug and are similar to the corrected cure rates in the clinically evaluable per protocol population shown in Table 12. For each subset, cure rates for Ciprodex patients are approximately 3% to 6% greater than those for Cortisporin patients.

6.1.3.2.4.3.2. Microbiologic Efficacy

Table 15 shows the proportions of patients with satisfactory microbiologic outcomes in evaluable subsets.

Table 15. Microbiologic Outcomes at Test of Cure Visit (Per Protocol)

Microbiologic Subset	Ciprodex n/m	Ciprodex (%)	Cortisporin n/m	Cortisporin (%)
PA/SA	118/126	(93.7)	106/123	(86.2)
PA/SA/GN	128/136	(94.1)	121/140	(86.4)
Proposed label	137/145	(94.5)	126/145	(86.9)
Applicant MPP	158/172	(91.9)	146/171	(85.4)

n/m = number with eradication or presumed eradication/number evaluable
PA/SA: *P. aeruginosa* or *S. aureus*
PA/SA/GNR: *P. aeruginosa*, *S. aureus*, or other Gram-negative bacteria
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's modified per protocol population
Adapted from 5/5/03 submission, Tables 9b, 13b, 17b, and 21b

Comment: The microbiologic outcome rates are similar across subsets for each drug and correspond closely to the clinical outcome rates. For each subset, eradication and presumed eradication rates for Ciprodex patients are approximately 6% to 8% greater than those for Cortisporin patients.

Pathogen Eradication Rates

Table 16 shows microbiologic response rates for each of the organisms in the applicant's proposed label.

Table 16. Microbiologic Response Rates by Baseline Isolate (Per Protocol)

Baseline Isolate	Ciprodex n/m	(%)	Cortisporin n/m	(%)
Gram-positive				
Staphylococcus aureus	21/23	(91)	10/13	(77)
Gram-negative				
Pseudomonas aeruginosa	99/105	(94)	97/112	(87)

n/m = number with eradication or presumed eradication/number evaluable
Adapted from 5/30/03 submission, Corrected Table 5b

Comment: The response rates for P. aeruginosa and S. aureus in the Ciprodex patients are consistent with the overall microbiologic response rates shown in Table 15. Most of the other organisms in the proposed label were isolated infrequently in this study.

6.1.3.2.5. Study Conclusions

In this study, Ciprodex was noninferior to Cortisporin for the primary endpoint of clinical response at TOC. Microbiologic outcomes support the clinical findings.

6.1.4. Indication Summary and Conclusions

The applicant has submitted two studies demonstrating that Ciprodex is noninferior to the approved comparator Cortisporin for the treatment of AOE. Protocol C-98-18 did not demonstrate the superiority of the combination over ciprofloxacin alone, however. The data presented in this NDA would not support the approvability of this combination product if it was being evaluated only for the AOE indication.

The question of optimal therapy for AOE, including the need for anti-inflammatory activity, is complicated. The efficacy of Cortisporin or of its components for the treatment of AOE, while generally accepted, is not well-established. Cortisporin otic solution was approved in 1975 based on a nonblinded comparison with Cortisporin otic suspension in which 58 patients received solution and 38 received suspension. Of patients with either *S. aureus* or *P. aeruginosa* isolated on entry, 74% of solution recipients and 69% of suspension recipients were considered "cleared" at follow-up out to 14 days after initiation of therapy. The review states that while comparative studies of hydrocortisone versus the antibiotic component would be desirable, "however, we had

previously decided that this was not feasible in the case of Cortisporin otic drops [suspension]." (review of NDA 50-479)

In the more recently approved Cipro HC NDA (NDA 20-805), a benefit of combination therapy for AOE was demonstrated in only one of two studies. The added benefit of the hydrocortisone component of Cipro HC was accepted on the basis of a single U.S. study that showed a statistically significant 21-hour reduction in median time to end of ear pain in patients who received Cipro HC compared with those receiving ciprofloxacin alone. The second study in this application was conducted in Europe and failed to demonstrate a contribution of elements using the same endpoint.

Practical reasons to consider approval of Ciprodex include the finding from these studies that Ciprodex is at least as effective as Cortisporin in the treatment of AOE. It is also likely to have efficacy similar to the related product, Cipro HC. Ciprodex has a greater concentration of ciprofloxacin (0.3% vs. 0.2%), and 0.1% dexamethasone is approximately two to three times more potent than 1% hydrocortisone. These preparations have not been compared directly, however.

For the AOMT indication, superiority of Ciprodex to ciprofloxacin alone was demonstrated for a clinically significant endpoint, time to cessation of otorrhea. This finding, coupled with the noninferiority to the approved combination product, Cortisporin, that was demonstrated in the AOE studies, supports approval of Ciprodex for the AOE indication.

Labeling

For the AOE indication, the **INDICATIONS AND USAGE** section of the label should include only those organisms that have clearly been demonstrated to have a significant role in this condition.

Cortisporin is approved "for the treatment of superficial bacterial infections of the external auditory canal, caused by organisms susceptible to the action of the antibiotics;" no specific organisms are listed under **INDICATIONS AND USAGE**. Cipro HC is approved for the treatment of AOE due to susceptible strains of *P. aeruginosa*, *S. aureus*, and *Proteus mirabilis*. Ofloxacin otic solution is approved for AOE due to *S. aureus* and *P. aeruginosa*.

AOE is generally diagnosed clinically and treated empirically. Cultures are rarely obtained in the office setting. Historically, *P. aeruginosa* and *S. aureus* have been regarded as the most significant pathogens associated with AOE. Literature surveys, the recent ofloxacin and Cipro HC submissions, and the current application report a large number of potential pathogens. For example, the applicant submitted a published review of the microbiology of AOE that incorporated the studies in this NDA along with other AOE studies they performed (Roland and Stroman 2002). In these studies, conducted from 1998 to 2000, the authors report the recovery of 2838 bacterial isolates, representing 202 species, from 2048 ears with AOE. The external auditory canal is a nonsterile site,

however, and it is often difficult to distinguish whether a given isolate is pathogenic or not. The draft guidance on uncomplicated and complicated skin and skin structure infections addresses the general issue of attributing pathogenicity to isolates and is applicable to this situation. For uncomplicated skin infections, sponsors are advised to provide scientific justification for considering organisms other than *S. aureus* and group A streptococci to be pathogens. In addition, the guidance also emphasizes the importance of proper collection of microbiologic specimens, including vigorous debridement before obtaining swabs of superficial infections.

Unfortunately, in this NDA, the protocols mandated collection of culture specimens from the external auditory canal wall before mechanical cleansing. The culture techniques used in these studies do not permit a distinction to be made between true pathogens and the overgrowth of normal flora or colonizers.

The applicant's approach to defining pathogens in AOE was based on a comparison of isolates from healthy ear canals with isolates from patients with AOE. The applicant characterized the microbiology of the normal external auditory canal in a study of healthy subjects (Stroman et al. 2001). Of 302 isolates from 147 ear canals, 96% were Gram-positive; the most common isolates were *Staphylococcus auricularis*, *Staphylococcus epidermidis*, *Staphylococcus capitis*, *Staphylococcus warneri*, *Turicella otitidis*, and *Alloiococcus otitis*. These organisms were considered nonpathogenic in the AOE NDA studies, and any other isolates (including
as discussed below) were considered pathogenic.

In the combined AOE studies in this NDA, there were 1385 positive ear cultures; 32% of the specimens grew more than one organism. There were 1929 pretherapy isolates, of which 1148 (59.5%) were categorized as Gram-negative pathogens, 614 (31.8%) as Gram-positive pathogens, 128 (6.6%) as nonpathogens, and 39 (2.0%) as fungi or yeast.

The applicant has listed in the proposed label, and the significance of many of these organisms is unclear. The division therefore asked the applicant to provide scientific justification for the inclusion of bacteria other than *P. aeruginosa* and *S. aureus*. Table 17 lists the proposed organisms along with the microbiologic response rates for Ciprodex-treated patients in the AOE studies.

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Table 17. Pathogen Eradication Rates for Ciprodex-Treated Patients: Combined AOE Studies (Per Protocol)

Baseline Isolate	C-98-18 n/m (%)	C-98-19 n/m (%)	Total n/m (%)
Gram-positive			
Staphylococcus aureus	17/18 (94)	21/23 (91)	38/41 (93)
Gram-negative			
Pseudomonas aeruginosa	124/144 (86)	99/105 (94)	223/249 (90)

n/m = number with eradication or presumed eradication/number evaluable
Adapted from 5/5/03 submission, Table 5a, and 5/30/03 submission, Corrected Table 5b

As expected, the most commonly isolated organisms in the AOE studies were *P. aeruginosa* (830 isolates; 43.0% of total) and *S. aureus* (119 isolates; 6.2%). *P. aeruginosa* was the only isolate in 67% of the specimens from which it was recovered; *S. aureus* was the only isolate in 43%. These organisms are appropriately included in the labeling for the AOE indication because of the frequency with which they are recovered, the demonstration of adequate treatment efficacy, and their well-characterized associations with AOE and other skin and soft tissue infections (including malignant otitis externa in the case of *P. aeruginosa*).

1 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Isolation of an organism is necessary but not sufficient evidence of pathogenicity, and for most of the organisms in the proposed label, additional information is needed to determine whether they are true pathogens in AOE. Evaluation of mixed culture results from swab specimens in this condition is complicated by the presence of indigenous flora in many cases and by the presence of acknowledged primary pathogens in others. Until the role of these proposed pathogens is better established, this reviewer recommends that labeling for this indication be limited to *P. aeruginosa* and *S. aureus*, the two pathogens most conclusively associated with AOE.

The applicant proposes that the labeling i

The **Clinical Efficacy** section of the label presents clinical and microbiologic efficacy rates based on the applicant's original per protocol analysis, which excluded patients who discontinued therapy because of treatment failure. This section should be revised to incorporate these patients and present a more accurate description of drug efficacy.

In the combined AOE studies, only 3 children under 2 years of age were treated with Ciprodex; the lower age limit in both studies was 1 year. The applicant has proposed a

lower age limit of 6 months in the label for the AOE indication. This corresponds with the lower age limit proposed for the AOMT indication.

Comment: There are adequate data to support use in children down to 6 months of age for AOMT; this age limit is acceptable for AOE.

References

1. Funke G, Haase G, Schnitzler N, Schrage N, Reinert RR. Endophthalmitis due to *Microbacterium* species: case report and review of microbacterium infections. Clin Infect Dis 1997; 24:713-716.
2. Roland PS, Stroman DW. Microbiology of acute otitis externa. Laryngoscope 2002; 112:1166-1177.
3. Stroman DW, Roland PS, Dohar J, Burt W. Microbiology of normal external auditory canal. Laryngoscope 2001; 111:2054-2059.

6.2. Acute Otitis Media in Patients with Tympanostomy Tubes

6.2.1. Conclusions and Critical Differences from Proposed Label Claims

The applicant has submitted two studies demonstrating that Ciprodex is effective for the treatment of AOMT. Protocol C-99-59 showed that the combination product was superior to ciprofloxacin alone for a clinically significant endpoint, time to cessation of otorrhea. Protocol C-00-52 showed noninferiority to the approved comparator ofloxacin. These studies support approval of Ciprodex for the AOMT indication.

The applicant's proposed label claims for the AOMT indication follow:

INDICATIONS AND USAGE

[redacted]

The following is excerpted from the **Clinical Efficacy** section:

6.2.2. General Approach to Review of Efficacy

The applicant performed two clinical efficacy trials to support the AOMT indication. Protocol C-99-59 compared Ciprodex with ciprofloxacin alone for the treatment of AOMT. This trial was intended to demonstrate superiority of the combination product to ciprofloxacin alone in time to cessation of otorrhea. Protocol C-00-52 compared Ciprodex with ofloxacin and was intended to demonstrate noninferiority of Ciprodex in clinical and microbiologic responses at the test of cure visit. These trials are reviewed in detail in the sections that follow.

6.2.3. Detailed Review of Trials

6.2.3.1. Protocol C-99-59: "Safety and Efficacy of Topical CIPRODEX® (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to CILOXAN® (Ciprofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT)"

6.2.3.1.1. Objectives

> The objective is to evaluate the efficacy and safety of topical CIPRODEX Suspension in AOMT patients; and to demonstrate therapeutic superiority of CIPRODEX relative to CILOXAN for cessation of otorrhea (primary). (Module 5, Vol. 3, p.309)

6.2.3.1.2. Design: Randomized (1:1), patient-masked, comparative, multicenter trial

> *Comment: The applicant stated that because of the physical differences between a suspension and a solution, investigators may not have been completely blinded.*

6.2.3.1.3. Protocol Overview

The original version of this protocol was dated 12/15/99. The study initiation date was 3/10/00, and the completion date was 2/2/01. There were two amendments. The first amendment, dated 2/2/00, modified two inclusion and exclusion criteria and added a procedure to detect the presence of ciprofloxacin in the nasopharynx after a single dose at a subset of study sites. The second amendment, dated 5/8/00, increased the number of study sites to facilitate enrollment of the planned number of patients.

A summary of the final version of this protocol follows.

6.2.3.1.3.1. Population

6.2.3.1.3.1.1. Inclusion Criteria

Patients enrolled in this study had to be between 6 months and 12 years of age, have otorrhea for 3 weeks or less, and have patent tympanostomy tubes.

6.2.3.1.3.1.2. Exclusion Criteria

Noteworthy exclusion criteria were:

1. Tympanostomy tube placement 3 days or less before study entry
2. Tympanostomy tubes containing silver oxide or silver salts; T-type tubes
3. Acute otitis externa or malignant otitis externa
4. Suspected viral, fungal, or mycobacterial ear infection
5. Otologic surgery within the previous year (other than tympanostomy tube placement)
6. History of an immunosuppressive disorder, current immunosuppressive therapy, or diabetes
7. Craniofacial anomalies
8. Use of topical nonsteroidal otic agents within 1 day of study entry
9. Use of topical otic steroids within 3 days of enrollment or systemic steroids within 7 days of enrollment
10. Concurrent use of intranasal or inhaled steroids that have significant systemic absorption
11. Any infection requiring systemic antimicrobial therapy
12. Use of topical or systemic antimicrobial agents within 2 to 14 days of enrollment (washout period varied depending on agent)
13. Concurrent use of oral or topical antiinflammatory agents

In addition to these exclusion criteria, patients with baseline cultures growing group A streptococci were to be discontinued from the study and treated with systemic therapy.

> *Comment: Patients with group A streptococcal AOMT were excluded from the ofloxacin studies because of the belief that inadequate treatment could lead to adverse outcomes like mastoiditis.*

6.2.3.1.3.2. Study Procedures

6.2.3.1.3.2.1. Study Drug Administration

Patients were randomized to receive one of the following study treatments:

- Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) suspension, 3 drops instilled into the affected ear(s) bid for 7 days

- Ciloxan (ciprofloxacin 0.3%) solution, 3 drops instilled into the affected ear(s) bid for 7 days

Comment: Note that the dose of Ciprodex in the proposed label is 4 drops bid for 7 days.

6.2.3.1.3.2.2. Study Evaluations

1. Visit 1 (Baseline; Day 1)
- Collection of general patient information
- Clinical assessment, including the following characteristics:
  - Otorrhea (present, absent)
  - Granulation tissue (none, mild, moderate, severe)
  - Characteristics of otorrhea (color/type, volume)
  - Tube patency (open, closed)
- Collection of culture specimen after cleansing of external auditory canal
- Tympanometry
- Audiologic evaluation for patients 4 to 12 years
- Dispensation of study drug and administration of first dose
- Testing for nasopharyngeal fluorescence and taste (at selected study sites)
- Distribution of patient diary

2. Visit 2 (During Therapy; Day 3 + 2)
- Clinical assessment
  - Clinical response (4-point scale: resolved, improved, not changed, worsened)
  - Granulation tissue
  - Characteristics of otorrhea
  - Tube patency
- Review of patient diary and transcription of information onto case report forms

3. Visit 3 (End of Therapy; Day 8 + 2)
- Clinical assessment
- Review of patient diary and transcription of information onto case report forms
- Collection of remaining study medication

4. Visit 4 (Test of Cure; Day 14 + 3)
- Clinical assessment
- Collection of culture specimen if otorrhea present
- Audiologic evaluation for patients 4 to 12 years
- Completion of exit form

6.2.3.1.3.3. Evaluability Criteria

The following evaluability criteria are taken directly from the Biostatistics Analysis Plan (Module 5, Vol. 4):

> All patients who receive treatment and have at least one on-therapy visit will be included in the intent to treat analysis. (p.534)
>
> *Comment: This ITT definition does not include all randomized patients.*
>
> All patients who receive treatment will be included in the safety analysis. (p.535)
>
> All patients who received treatment, met inclusion/exclusion criteria and had at least one on-therapy visit will be included in the Per Protocol analysis. Individual patient visits may be excluded if inclusion/exclusion criteria (such as use of contraindicated concomitant medications) are violated at only a subset of the patient's visits and such violations, in the opinion of the medical monitor, do not invalidate the remaining visits. (p.535)
>
> All data obtained will be used in the analysis. Otorrhea will be considered to be present throughout the study with right censoring occurring at the time of discontinuation for patients who terminate the study early without resolution of otorrhea. No data will be imputed. (p.535)

Microbiologic procedures were defined in a nonclinical study protocol that was appended to the clinical protocol. The microbiology protocol section entitled "Defined Pathogens in Patients with Acute Otorrhea" states that expected isolates "include but are not limited to the following:"

> Gram-Positive Aerobic Bacteria
>
> *Staphylococcus*
> *Streptococcus*
>
> Gram-Negative Aerobic Bacteria
>
> *Pseudomonas*
> *Haemophilus*
> *Moraxella*

In addition, "Other microorganisms present may also be considered as 'pathogens.'" (Module 5, Vol. 4, p.414)

Comment:

6.2.3.1.3.4. Endpoints

The primary clinical efficacy variable under analysis is time to cessation of otorrhea. Otorrhea will be defined as ending on the first day on which the otorrhea is absent and remains absent for all subsequent diary entries. (Module 5, Vol. 3, p.327)

The secondary efficacy variables are clinical response, antimicrobial response, and reduction of granulation tissue. (Module 5, Vol. 4, p.533)

6.2.3.1.3.5. Statistical Considerations

Kaplan-Meier survival curves were to be constructed to evaluate the difference in median time to cessation of otorrhea. The applicant assumed that the median time to cessation of otorrhea in patients receiving Ciprodex was approximately 3.4 days. At least 75 clinically evaluable patients per group were needed to provide 80% probability of detecting a 2-day difference in median time to cessation of otorrhea.

6.2.3.1.4. Study Results

6.2.3.1.4.1. Demographics

Two hundred one patients were randomized to receive one of the study therapies: 103 to receive Ciprodex and 98 to receive Ciloxan. Eighteen U.S. sites enrolled patients, with no site enrolling more than 15% of the total. Table 18 shows the baseline characteristics of the randomized patients.

Table 18. Baseline Patient Characteristics

	Ciprodex (N=103)		Ciloxan (N=98)		Total (N=201)	
	n	(%)	n	(%)	n	(%)
Age						
1-23 months	49	(47.6)	52	(53.1)	101	(50.2)
2-11 years	52	(50.5)	46	(46.9)	98	(48.8)
12-17 years	2	(1.9)	-	-	2	(1.0)
Mean (years)	2.6		2.2		2.4	
Range (years)	0 to 12		0 to 11		0 to 12	
Sex						
Male	59	(57.3)	53	(54.1)	112	(55.7)
Female	44	(42.7)	45	(45.9)	89	(44.3)
Race						
White	85	(82.5)	78	(79.6)	163	(81.1)
Black	8	(7.8)	8	(8.2)	16	(8.0)
Other	10	(9.7)	12	(12.2)	22	(10.9)

Adapted from C-99-59 study report, Volume 3, Tables 11.2-2 and 11.2-3

Comment: The distribution of baseline characteristics was similar for each of the randomized groups.

6.2.3.1.4.2. Evaluability

Table 19 shows the applicant's determinations of patient evaluability.

Table 19. Applicant's Accounting of Patient Evaluability

	Ciprodex (N=103)		Ciloxan (N=98)	
	n	(%)	n	(%)
ITT Evaluable	100	(97.1)	92	(93.9)
ITT Unevaluable	3	(2.9)	6	(6.1)
No on-therapy follow-up data	3		6	
Per Protocol Evaluable	80	(77.7)	61	(62.2)
Per Protocol Unevaluable	20	(19.4)	31	(31.6)
Exclusion criteria	4		2	
Excluded concomitant medication	7		19	
Protocol violation	-		3	
Excluded concomitant disease	1		-	
TOC visit outside specified range	4		2	
Missed visit	6		7	

TOC = Test of Cure
Two patients in each group had two reasons for unevaluability.

Adapted from C-99-59 study report, Volume 3, Table 10.1-3

Comment: This medical officer performed a blinded review of 30% of the CRFs (approximately 30 CRFs in each treatment group) to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with investigators' evaluability and outcome assessments. This reviewer found that the key data transcriptions were accurate. Review of the CRFs of patients who were deemed unevaluable because of "excluded concomitant medication" revealed that many of these cases were actually treatment failures who were discontinued from the study and prescribed alternative therapy, which made them unevaluable for the per protocol analysis. If these patients returned for follow-up and were rated as cured, they were considered to be cures in the applicant's ITT analysis. These cases were accurately labeled as treatment failures on the CRFs; in the ITT population, there were 4 Ciprodex failures and 14 Ciloxan failures. The applicant discusses these cases separately in the study report section on primary efficacy analyses. The applicant's approach inflates the apparent clinical efficacy of the study treatments. From the Agency's standpoint, these cases should be included as failures in the per protocol and ITT analyses. On 4/4/03, the division asked the applicant to submit corrected analyses which incorporated treatment failures into the test-of-cure outcomes. The revised figures that were submitted have been reviewed and are acceptable. In presenting test-of-cure efficacy data, both the applicant's original and corrected results are shown. Correcting the analyses to account for treatment failures provides a more accurate description of drug efficacy.

6.2.3.1.4.3. Efficacy

6.2.3.1.4.3.1. Clinical Efficacy

The primary objective of this study was to demonstrate the superiority of the combination product to ciprofloxacin alone in time to cessation of otorrhea. The median time to cessation of otorrhea in the Ciprodex group was 4 days and in the Ciloxan group was 5 days. This finding was consistent for each of the applicant's analysis populations (ITT, per protocol, and modified ITT and per protocol), with *p*-values for the differences in median duration ranging from 0.0002 to 0.0047 (survival analysis using log-rank test). Table 20 shows the results for the ITT analysis.

Table 20. Time to Cessation of Otorrhea (ITT)

	Ciprodex (n=100)	**Ciloxan (n=92)**
Mean (d)	4.14	5.41
Median (d)	4.00	5.00
Standard deviation (d)	1.98	2.00
Range (d)	2 to 10	2 to 10
p = 0.0002 for difference in median time to cessation of otorrhea (log-rank test, Kaplan-Meier survival analysis)		

Adapted from C-99-59 study report, Volume 3, Table 14.2-1

Comment: The analysis of time to cessation of otorrhea is not affected by the evaluability and test-of-cure outcome issues discussed in the previous section. In fact, a statistically significant difference between treatments is present even when the failures, which occurred disproportionately in the Ciloxan group, are excluded. A 1-day difference in median time to cessation of otorrhea is clinically significant as well.

Table 21 shows the proportions of patients who were rated as cured in the applicant's original and corrected per protocol analyses. Cure rates in the applicant's original per protocol analysis were 95.0% for Ciprodex and 98.4% for Ciloxan, and in the corrected analysis, cure rates were 90.5% and 79.5%, respectively.

Table 21. Clinical Outcomes at Test of Cure Visit (Per Protocol)

	Ciprodex		Ciloxan			
Per Protocol Analysis	n/m	(%)	n/m	(%)	Diff	95% CI
Original	76/80	(95.0)	60/61	(98.4)	-3.4	*
Corrected	76/84	(90.5)	58/73	(79.5)	11.0	-0.2, 22.2

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions;
* 95% CI not reported by applicant; p = 0.8141, Cochran-Mantel-Haenszel rank scores test

Adapted from C-99-59 study report, Volume 3, Table 14.2-5, and 5/5/03 submission, Table 3c

Comment: Because of the greater number of treatment failures in the Ciloxan group, correction of the per protocol outcomes in the revised analysis had a significant effect on the comparison between treatments.

Table 22 shows the proportion of patients who were rated as cured in the original and corrected ITT analyses. Cure rates in the applicant's original ITT analysis were 91.0% for Ciprodex and 89.1% for Ciloxan, and in the corrected analysis, cure rates were 89.0% and 76.1%, respectively.

Table 22. Clinical Outcomes at Test of Cure Visit (ITT)

	Ciprodex		Ciloxan			
ITT Analysis	n/m	(%)	n/m	(%)	Diff	95% CI
Original	91/100	(91.0)	82/92	(89.1)	1.9	*
Corrected	89/100	(89.0)	70/92	(76.1)	12.9	2.3, 23.6

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions;
* 95% CI not reported by applicant; $p = 0.1769$, Cochran-Mantel-Haenszel rank scores test

Adapted from C-99-59 study report, Volume 3, Table 14.2-4, and 5/5/03 submission, Table 2c

Comment: Again, because of the greater number of treatment failures in the Ciloxan group, correction of the ITT outcomes in the revised analysis had a significant effect on the comparison between treatments. In this case, the 95% CI around the treatment difference is greater than 0.

One of the secondary objectives of this study was to demonstrate the superiority of the combination product to ciprofloxacin alone in reduction of granulation tissue at each visit. Granulation tissue was present at baseline in only approximately 20% of patients. No significant differences between treatments were noted in reduction of granulation tissue at any of the follow-up visits.

Microbiologically Evaluable Patients

Comment: The applicant's original analysis considered "defined pathogens" to include a number of organisms of uncertain pathogenicity in AOMT. On 4/4/03, the division asked the applicant to perform exploratory analyses on several subsets of microbiologically evaluable patients using the revised per protocol and ITT populations. The requested subsets included: patients with Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis, or Pseudomonas aeruginosa (all well-established pathogens in AOMT); patients with any organism in the proposed label; and patients with any organism. The last population is equivalent to the applicant's revised modified per protocol population. The analyses of subsets of isolates submitted in response considered "only the eradicated pre-therapy isolates from patients categorized as 'successes' and the persisting pre-therapy isolates from patients categorized as 'failures'" (5/5/03 response, p.7). Patients with microbiologic outcomes such as superinfection and reinfection were excluded. This reviewer believes that patients with these outcomes should be included in the analyses. The review of the AOE indication used this approach. In a teleconference on 5/23/03, the applicant agreed to submit lists of patients who had been excluded from isolate level analyses. In the analyses presented in this review (clinical outcomes in microbiologically evaluable patients, microbiologic outcomes, and per pathogen outcomes), the medical officer has modified the tables submitted by the applicant

to include all microbiologically evaluable patients in each subset. Patients with microbiologic outcomes other than eradication or presumed eradication are considered to be failures.

Table 23 shows the proportions of patients rated as cured in subsets of microbiologically evaluable patients.

Table 23. Clinical Outcomes in Microbiologically Evaluable Subsets (Per Protocol)

	Ciprodex		Ciloxan	
Microbiologic Subset	n/m	(%)	n/m	(%)
SP/SA/HI/MC/PA	43/48	(89.6)	34/45	(75.6)
Proposed label	58/64	(90.6)	43/55	(78.2)
Applicant MPP	65/73	(89.0)	51/64	(79.7)

n/m = number of cures/number evaluable
SP/SA/HI/MC/PA: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa*
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 27a, 31a, and 35a

Comment: Cure rates are similar across subsets for each drug and are similar to the corrected cure rates in the clinically evaluable per protocol population shown in Table 21. For each subset, cure rates for Ciprodex patients are approximately 9% to 14% greater than those for Ciloxan patients.

6.2.3.1.4.3.2. Microbiologic Efficacy

Table 24 shows the proportions of patients with satisfactory microbiologic outcomes in evaluable subsets.

Table 24. Microbiologic Outcomes at Test of Cure Visit (Per Protocol)

	Ciprodex		Ciloxan	
Microbiologic Subset	n/m	(%)	n/m	(%)
SP/SA/HI/MC/PA	43/48	(89.6)	34/45	(75.6)
Proposed label	59/64	(92.2)	43/55	(78.2)
Applicant MPP	66/73	(90.4)	51/64	(79.7)

n/m = number with eradication or presumed eradication/number evaluable
SP/SA/HI/MC/PA: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa*
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 25a, 29a, and 33a

Comment: The microbiologic outcome rates are similar across subsets for each drug and correspond closely to the clinical outcome rates. For each subset, eradication and presumed eradication rates for Ciprodex patients are approximately 10% to 14% greater than those for Ciloxan patients.

Pathogen Eradication Rates

Table 25 shows the microbiologic response rates for each of the organisms in the applicant's proposed label.

Table 25. Microbiologic Response Rates by Baseline Isolate (Per Protocol)

Baseline Isolate	Ciprodex n/m	Ciprodex (%)	Ciloxan n/m	Ciloxan (%)
Gram-positive				
Staphylococcus aureus	17/17	(100)	10/12	(83)
Streptococcus pneumoniae	16/21	(76)	13/19	(68)
Gram-negative				
Haemophilus influenzae	4/4	(100)	8/9	(89)
Moraxella catarrhalis	4/4	(100)	-	-
Pseudomonas aeruginosa	11/11	(100)	8/13	(62)

n/m = number with eradication or presumed eradication/number evaluable

Adapted from 5/5/03 submission, Table 5c

Comment: S. pneumoniae was the only isolate in the Ciprodex group for which the microbiologic response rate was not 100%. The 5 failures included 3 with documented persistence, 1 with presumed persistence in which no specimen was collected, and 1 with presumed persistence in a treatment failure with a sterile culture.

6.2.3.1.5. Study Conclusions

In this study, the applicant demonstrated that Ciprodex is superior to ciprofloxacin alone in time to cessation of otorrhea; the 1-day reduction in duration of otorrhea is both statistically and clinically significant. The applicant was unable to demonstrate superiority of the combination in reduction of granulation tissue. For the other test-of-cure clinical and microbiologic endpoints, Ciprodex was noninferior to ciprofloxacin alone. The test-of-cure data are suggestive that the combination is better, but this trial was not designed to demonstrate superiority for these endpoints.

6.2.3.2. Protocol C-00-52: "Safety and Efficacy of Topical CIPRODEX Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to FLOXIN® Otic (Ofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT)"

6.2.3.2.1. Objectives

The objective is to evaluate the efficacy and safety of topical CIPRODEX Suspension in AOMT patients; and to demonstrate the noninferiority of CIPRODEX Otic Suspension relative to FLOXIN Otic Solution in clinical and microbiologic response at the test of cure (TOC) visit. (Module 5, Vol. 8, p.468)

6.2.3.2.2. Design: Randomized (1:1), observer-masked, comparative, multicenter trial

Comment: Because of the physical differences between a suspension and a solution and because of differences in the daily dosage and treatment duration in the two arms, investigators may not have been completely blinded.

6.2.3.2.3. Protocol Overview

The original version of this protocol was dated 11/20/00. The study initiation date was 2/14/01, and the completion date was 5/20/02. There were two amendments. The first amendment, dated 1/31/01, changed the timing of the end of therapy and test of cure visits so that they occurred on the same postrandomization day for each study arm. The second amendment, dated 10/23/01, increased the minimum enrollment age for Canadian patients from 6 months to 1 year. This change was requested by Canadian regulatory authorities because the comparator, ofloxacin otic solution, was approved only for patients aged 1 to 12 years.

A summary of the final version of this protocol follows.

6.2.3.2.3.1. Population

6.2.3.2.3.1.1. Inclusion Criteria

Patients enrolled in this study had to be between 6 months and 12 years of age, have otorrhea for 3 weeks or less, and have patent tympanostomy tubes.

6.2.3.2.3.1.2. Exclusion Criteria

The exclusion criteria were the same as in C-99-59 (see section 6.2.3.1.3.1.2., p.47).

6.2.3.2.3.2. Study Procedures

6.2.3.2.3.2.1. Study Drug Administration

Patients were randomized to receive one of the following study treatments:

- Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) suspension, 4 drops instilled into the affected ear(s) bid for 7 days
- Ofloxacin 0.3% solution, 5 drops instilled into the affected ear(s) bid for 10 days

6.2.3.2.3.2.2. Study Evaluations

Study evaluations were the same as in C-99-59 (see section 6.2.3.1.3.2.2., p.49), except that there was no testing for nasopharyngeal fluorescence and taste and the end of therapy and test of cure visits were on days 11 + 2 and 17 + 3, respectively.

6.2.3.2.3.3. Evaluability Criteria

> All patients who receive drug will be evaluable for safety analyses. All randomized patients will be evaluable for intent-to-treat (ITT) analyses. All patients who receive drug, meet inclusion criteria and are culture positive for bacteria on Day 1 will be evaluable for the modified intent-to-treat (MITT) analyses. For both ITT and MITT, patients who have no measurements after baseline are included as treatment failures. All patients who comply with the protocol, receive study drug and are present for all study visits will be evaluable for the per protocol (PP) analyses. All PP patients who are culture positive for bacteria on Day 1 will be evaluable for the modified per protocol (MPP) analyses. (Module 5, Vol. 8, pp.488-489)

On 6/7/02, the applicant modified the Biostatistics Efficacy Analysis Plan to allow the PP and MPP analyses to include patients with missed visits:

> All patients who receive drug, meet inclusion criteria and exclusion criteria and have baseline and Test-of-Cure (or exit if patient exited from the study early) visits are evaluable for the per protocol analysis. (Module 5, Vol. 9, p.848)

> *Comment: The applicant stated that this change was enacted before treatment masking was broken. With this change, patients who discontinued the study because of treatment failure would no longer be excluded from the PP and MPP analyses. This corrects one of the problems with the AOE studies and C-99-59, in which the analyses had to be revised to account for failures.*

The microbiologic procedures were the same as in C-99-59, with the addition of — to the list of "Defined Pathogens in Patients with Acute Otorrhea."

Comment: — *are not generally accepted pathogens in AOMT.*

6.2.3.2.3.4. Endpoints

> There are two primary efficacy variables under analysis in this study. The first variable is proportion of patients rated as resolved by the investigator for overall clinical response as measured on a 4-point scale (resolved=0, worsened=3) at the TOC visit. The second primary efficacy variable is proportion of patients for whom disease-specific pathogens are present at enrollment and absent at the TOC visit. (Module 5, Vol. 8, p.489)

6.2.3.2.3.5. Statistical Considerations

Assuming clinical cure rates at the test of cure visit of 80% for Ciprodex and 76.3% for ofloxacin, Alcon calculated that at least 191 clinically evaluable patients per group would provide 90% probability that the lower bound of the 95% confidence interval for the treatment difference between Ciprodex and ofloxacin would be greater than -10%.

6.2.3.2.4. Study Results

6.2.3.2.4.1. Demographics

Five hundred ninety-nine patients were randomized to receive one of the study therapies: 297 to receive Ciprodex and 302 to receive ofloxacin. Thirty-nine U.S. and Canadian sites enrolled patients, with no site enrolling more than 11% of the total. Table 26 shows the baseline characteristics of the randomized patients.

Table 26. Baseline Patient Characteristics

	Ciprodex (N=297)		Ofloxacin (N=302)		Total (N=599)	
	n	(%)	n	(%)	n	(%)
Age						
1-23 months	146	(49.2)	148	(49.0)	294	(49.1)
2-11 years	148	(49.8)	154	(51.0)	302	(50.4)
12-17 years	3	(1.0)	-	-	3	(0.5)
Mean (years)	2.5		2.4		2.4	
Range (years)	0 to 12		0 to 11		0 to 12	
Sex						
Male	172	(57.9)	201	(66.6)	373	(62.3)
Female	125	(42.1)	101	(33.4)	226	(37.7)
Race						
White	242	(81.5)	244	(80.8)	486	(81.1)
Black	16	(5.4)	17	(5.6)	33	(5.5)
Hispanic	26	(8.8)	28	(9.3)	54	(9.0)
Other	13	(4.4)	13	(4.3)	26	(4.3)

Adapted from C-00-52 study report, Volume 7, Tables 11.2-2 and 11.2-3

Comment: The proportion of males is greater in the ofloxacin arm.

6.2.3.2.4.2. Evaluability

Table 27 shows the applicant's determinations of patient evaluability.

Table 27. Applicant's Accounting of Patient Evaluability

	Ciprodex (N=297)		Ofloxacin (N=302)	
	n	(%)	*n*	(%)
Per Protocol Evaluable	232	(78.1)	220	(72.8)
Per Protocol Unevaluable	65	(21.9)	82	(27.2)
Exclusion criteria	4		8	
Excluded concomitant medication	1		6	
Excluded concomitant disease	3		-	
Culture positive for Group A streptococci	7		5	
Yeast at baseline	7		8	
Micro nonanalyzable	1		2	
Noncompliance	1		-	
TOC visit outside specified range	2		2	
Missed visit	38		51	

TOC = Test of Cure

Adapted from C-00-52 study report, Volume 7, Table 10.1-2

Comment: This medical officer performed a blinded review of 10% of the CRFs to verify the accuracy of the transcription of data from the CRFs to the database and to check for agreement with investigators' evaluability and outcome assessments. This reviewer found that the key data transcriptions and investigators' outcome assessments were accurate. Review of the CRFs of patients who were deemed unevaluable because of "missed visit" revealed that the majority of these cases were actually patients who were discontinued from the study because of the development of otitis media in the nonstudy ear or of other manifestations of upper respiratory infection. The prescription of alternative therapy in these cases made these patients unevaluable in the per protocol analysis.

In this protocol, patients with treatment failure were not excluded from the per protocol analysis. Because of the exclusion of failures in the AOE studies and in the initial AOMT study, however, the division asked the applicant to submit corrected analyses for all studies. The results of both analyses are presented below.

6.2.3.2.4.3. Efficacy

6.2.3.2.4.3.1. Clinical Efficacy

Table 28 shows the proportions of patients who were rated as cured in the applicant's original and corrected per protocol analyses. Cure rates in the applicant's original per protocol analysis were 87.9% for Ciprodex and 77.3% for ofloxacin, and in the corrected analysis, cure rates were 85.6% and 79.1%, respectively.

Table 28. Clinical Outcomes at Test of Cure Visit (Per Protocol)

	Ciprodex		Ofloxacin			
Per Protocol Analysis	n/m	(%)	n/m	(%)	Diff	95% CI
Original	204/232	(87.9)	170/220	(77.3)	10.7	3.7, 17.6
Corrected	202/236	(85.6)	174/220	(79.1)	6.5	-0.5, 13.5

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions
Adapted from C-00-52 study report, Volume 7, Table 11.4.1.1-1, and 5/5/03 submission, Table 3d

Comment: It was expected that the corrected per protocol analysis for this study would differ little, if any, from the original analysis. The findings from both analyses are very similar, although in the revised analysis, the lower limit of the 95% CI for the treatment difference is less than 0.

The applicant submitted subgroup analyses by age, sex, and race. Clinical outcomes for each subgroup were similar to those observed in the overall data.

Table 29 shows the proportion of patients who were rated as cured in the original and corrected ITT analyses. Cure rates in the applicant's original ITT analysis were 74.7% for Ciprodex and 61.3% for ofloxacin, and in the corrected analysis, cure rates were 76.1% and 65.9%, respectively.

Table 29. Clinical Outcomes at Test of Cure Visit (ITT)

	Ciprodex		Ofloxacin			
ITT Analysis	n/m	(%)	n/m	(%)	Diff	95% CI
Original	222/297	(74.7)	185/302	(61.3)	13.5	6.1, 20.9
Corrected	226/297	(76.1)	199/302	(65.9)	10.2	3.0, 17.4

n/m = number of cures/number evaluable
Diff = treatment difference (%); 95% CI = two-sided 95% confidence interval for difference in proportions
Adapted from C-00-52 study report, Volume 7, Table 11.4.1.1-1, and 5/5/03 submission, Table 2d

Comment: The differences between the original and corrected analyses are greater in the ITT analysis, particularly in the subset of patients who were per protocol unevaluable but ITT evaluable. The original analysis used an applicant-generated clinical outcome variable rather than the investigator's clinical impression. The data analysis plan stated, however, that the investigator's rating was to be used for determinations of clinical outcome. Examinations of the database and of the limited number of available CRFs reveal that in cases where the analyses are discrepant, the corrected analysis corresponds most closely to the investigators' final clinical assessments. The corrected analyses will be used for the primary endpoint and pathogen eradication discussions that follow. Note that for each ITT analysis, the treatment difference favors Ciprodex, and the lower limit of the 95% CI for the difference is greater than 0.

The applicant analyzed several secondary endpoints at each visit, including clinical response, granulation tissue, presence of otorrhea, volume of otorrhea, and color/type of otorrhea. Time to cessation of otorrhea was also analyzed. The applicant reported that Ciprodex is superior to ofloxacin in the following respects: improvement in clinical

response at days 3, 11, and 18 (days 3 and 11, all populations; day 18, ITT and MITT); absence of otorrhea at days 3, 11, and 18 (days 3 and 11, all populations; day 18, ITT and MITT); reduction in granulation tissue at days 11 and 18 (day 11, all populations; day 18, MITT only); reduction in otorrhea volume at days 3, 11, and 18 (days 3 and 11, all populations; day 18, ITT and MITT); "absence of otorrhea color and less purulent otorrhea at Day 3, and absence of otorrhea color and less mucoid otorrhea at Days 11 and 18" (days 3 and 11, all populations; day 18, ITT and MITT); and time to cessation of otorrhea (median duration, 4 days for all Ciprodex populations vs. 5 days for ofloxacin ITT and MITT and 6 days for PP and MPP).

The Clinical Efficacy subheading of the applicant's proposed label contains the statement, "

In this study, as in Protocol C-99-59, granulation tissue was present at baseline in approximately 20% of patients. At day 11, it was present in 3% to 4% of Ciprodex patients and in 13% to 14% of ofloxacin patients, with statistical significance reported for all populations. At day 18, it was present in 2% to 3% of Ciprodex patients and in 7% to 11% of ofloxacin patients, with statistical significance reported only for the MITT population.

> *Comment: This finding is from one of numerous interrelated secondary analyses and is not present in all analysis populations at TOC. The clinical significance of this treatment difference is unclear.*

Microbiologically Evaluable Patients

> *Comment: The approach to the analysis of microbiologically evaluable patients in this study is the same as that used for Protocol C-99-59 (see section 6.2.3.1.4.3.1, p.54). In the analyses that follow (clinical outcomes in microbiologically evaluable patients, microbiologic outcomes, and per pathogen outcomes), the medical officer has modified the tables submitted by the applicant to include all microbiologically evaluable patients in each subset. Patients with microbiologic outcomes other than eradication or presumed eradication are considered to be failures.*

Table 30 shows the proportions of patients rated as cured in subsets of microbiologically evaluable patients.

Table 30. Clinical Outcomes in Microbiologically Evaluable Subsets (Per Protocol)

	Ciprodex		Ofloxacin	
Microbiologic Subset	n/m	(%)	n/m	(%)
SP/SA/HI/MC/PA	109/126	(86.5)	102/129	(79.1)
Proposed label	133/151	(88.1)	117/150	(78.0)
Applicant MPP	162/181	(89.5)	135/170	(79.4)

n/m = number of cures/number evaluable
SP/SA/HI/MC/PA: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa*
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 27b, 31b, and 35b

Comment: Cure rates are similar across subsets for each drug and are similar to the corrected cure rates in the clinically evaluable per protocol population shown in Table 28. For each subset, cure rates for Ciprodex patients are approximately 7% to 10% greater than those for ofloxacin patients.

6.2.3.2.4.3.2. Microbiologic Efficacy

Table 31 shows the proportions of patients with satisfactory microbiologic outcomes in evaluable subsets.

Table 31. Microbiologic Outcomes at Test of Cure Visit (Per Protocol)

	Ciprodex		Ofloxacin	
Microbiologic Subset	n/m	(%)	n/m	(%)
SP/SA/HI/MC/PA	111/126	(88.1)	105/129	(81.4)
Proposed label	136/151	(90.1)	121/150	(80.7)
Applicant MPP	165/181	(91.2)	139/170	(81.8)

n/m = number with eradication or presumed eradication/number evaluable
SP/SA/HI/MC/PA: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Pseudomonas aeruginosa*
Proposed label: Any organism in proposed label
Applicant MPP: Applicant's revised modified per protocol population

Adapted from 5/5/03 submission, Tables 25b, 29b, and 33b

Comment: The microbiologic outcome rates are similar across subsets for each drug and correspond closely to the clinical outcome rates. For each subset, eradication and presumed eradication rates for Ciprodex patients are approximately 7% to 10% greater than those for ofloxacin patients.

Pathogen Eradication Rates

Table 32 shows the microbiologic response rates for each of the organisms in the applicant's proposed label.

Table 32. Microbiologic Response Rates by Baseline Isolate (Per Protocol)

Baseline Isolate	Ciprodex n/m	(%)	Ofloxacin n/m	(%)
Gram-positive				
Staphylococcus aureus	32/35	(91)	31/33	(94)
Streptococcus pneumoniae	23/24	(96)	32/38	(84)
Gram-negative				
Haemophilus influenzae	22/24	(92)	25/28	(89)
Moraxella catarrhalis	6/7	(86)	7/8	(88)
Pseudomonas aeruginosa	36/37	(97)	23/26	(88)

n/m = number with eradication or presumed eradication/number evaluable

Adapted from 5/5/03 submission, Table 5d

Comment: The response rates for common AOMT pathogens in the Ciprodex patients are consistent with the overall microbiologic response rates shown in Table 31. Most of the other organisms in the proposed label occurred infrequently in this study. Note that there were no isolates reported in this study.

6.2.3.2.5. Study Conclusions

In this study, Ciprodex was noninferior to the approved comparator ofloxacin for clinical and microbiologic endpoints at TOC in patients with AOMT.

6.2.4. Indication Summary and Conclusions

The applicant has submitted two studies demonstrating that Ciprodex is effective for the treatment of AOMT. Protocol C-99-59 showed that the combination product was superior to ciprofloxacin alone for a clinically significant endpoint, time to cessation of otorrhea. Protocol C-00-52 showed noninferiority to the approved comparator ofloxacin. These studies support approval of Ciprodex for the AOMT indication.

Labeling

The generally accepted pathogens in AOMT include the common causes of AOM, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, as well as the major causes of AOE, *P. aeruginosa* and *S. aureus* (Mandel et al. 1994). The only other product approved for this indication, ofloxacin otic solution, lists these organisms in the label.

In the original protocols for this indication, the applicant included
and " as "defined pathogens in acute otorrhea." No attempt was made to distinguish between pathogens and nonpathogens.

The applicant has listed n the proposed label, including none of which have been

generally considered to be pathogens in AOMT. The division therefore asked the applicant to provide scientific justification for the inclusion of these organisms in the label. Table 33 lists the proposed organisms along with the microbiologic response rates for Ciprodex-treated patients in the AOMT studies.

Table 33. Pathogen Eradication Rates for Ciprodex-Treated Patients: Combined AOMT Studies (Per Protocol Populations)

Baseline Isolate	C-99-59 n/m	(%)	C-00-52 n/m	(%)	Total n/m	(%)
Gram-positive						
Staphylococcus aureus	17/17	(100)	32/35	(91)	49/52	(94)
Streptococcus pneumoniae	16/21	(76)	23/24	(96)	39/45	(87)
Gram-negative						
Haemophilus influenzae	4/4	(100)	22/24	(92)	26/28	(93)
Moraxella catarrhalis	4/4	(100)	6/7	(86)	10/11	(91)
Pseudomonas aeruginosa	11/11	(100)	36/37	(97)	47/48	(98)

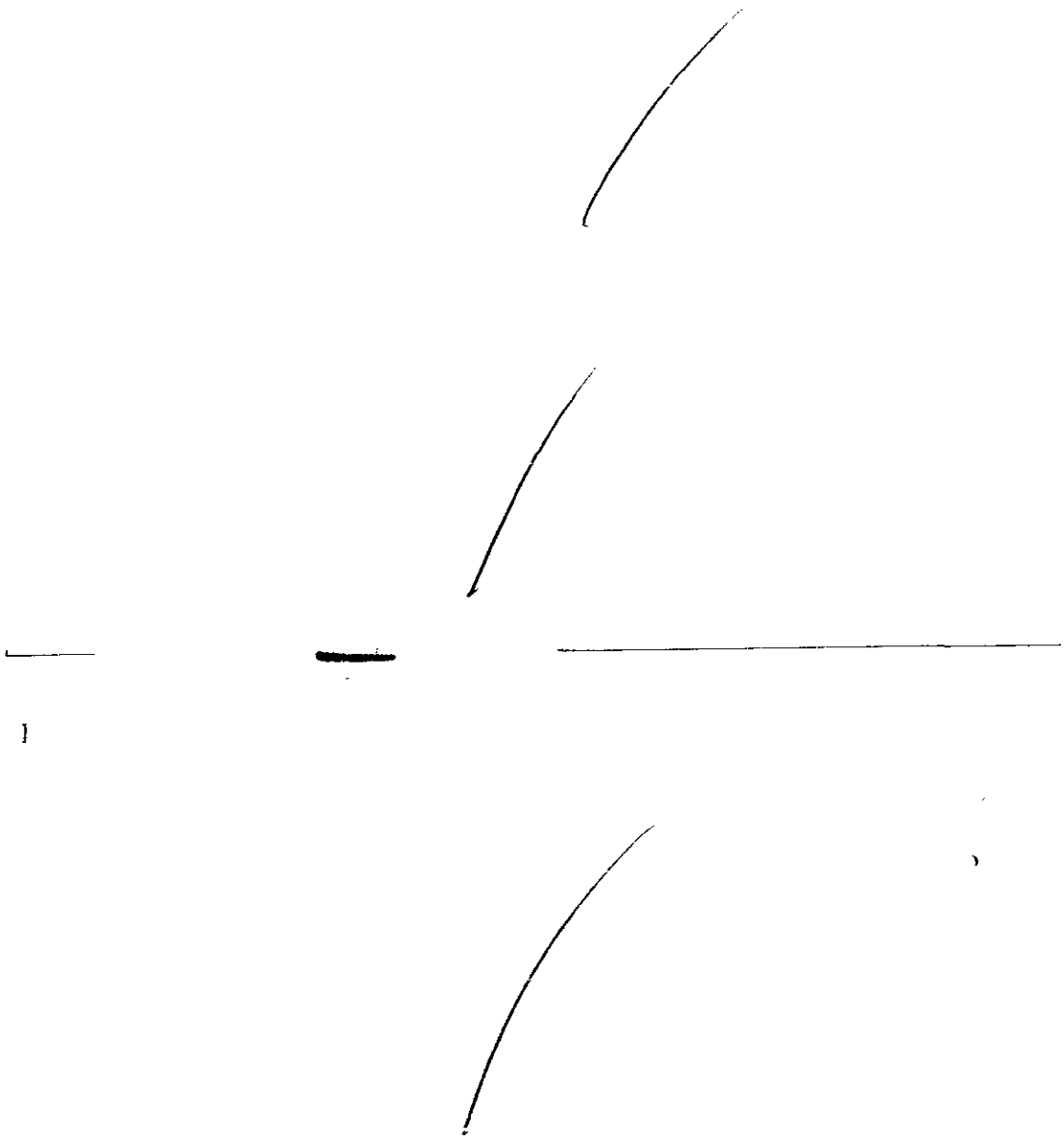
n/m = number with eradication or presumed eradication/number evaluable

Adapted from 5/5/03 submission, Tables 5c and 5d

S. aureus, *S. pneumoniae*, *H. influenzae*, and *P. aeruginosa* are generally recognized AOMT pathogens that were frequently recovered and for which Ciprodex demonstrated satisfactory eradication rates. Although there were relatively few *M. catarrhalis* isolates in Ciprodex-treated patients, this is a well-recognized pathogen in this condition and the eradication rate in Ciprodex-treated patients was satisfactory. These organisms are appropriately included in the label for this indication.

Several of the organisms in the proposed label are not generally considered to be pathogens in AOMT, and the data submitted are insufficient to make a determination about pathogenicity. Until the role of these proposed pathogens is established definitively, this reviewer recommends that the labeling for AOMT be limited to *S. aureus*, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *P. aeruginosa*.

The applicant proposes



The **Clinical Efficacy** section of the label presents clinical and microbiologic efficacy rates based on the applicant's original modified per protocol analysis. The population studied should be specified, and the rates cited should be based on the adjusted analyses. The claim for [redacted] should be deleted. This effect was not demonstrated in all analysis populations; at the test of cure visit, it was statistically significant only in the MITT population.

References

Mandel EM, Casselbrant ML, Kurs-Lasky M. Acute otorrhea: bacteriology of a common complication of tympanostomy tubes. Ann Otol Rhinol Laryngol 103:713-718.

7. Integrated Review of Safety

7.1. Detailed Review of Phase 2 and 3 Trials

Safety reviews are presented by indication. For each study presented, the safety analysis includes all patients who received at least one dose of study drug. At scheduled or unscheduled study visits, investigators were to inquire about adverse events and record their observations. The reporting period was through study exit at the test of cure visit 7 to 10 days following the completion of therapy.

7.1.1. Acute Otitis Externa

7.1.1.1. Protocol C-98-18: "Topical CILODEX (ciprofloxacin 0.3%, dexamethasone 0.1%) Suspension Compared to CILOXAN® (ciprofloxacin 0.3%) Solution and CORTISPORIN® Suspension (neomycin 0.35%, polymyxin 10,000 IU/mL, hydrocortisone 1.0%) for Treatment of Patients with Moderate to Severe Acute Otitis Externa (AOE)"

7.1.1.1.1. Extent of Exposure

In this study, 305 patients received Ciprodex, 305 patients received Ciloxan, and 299 patients received Cortisporin. The mean duration of treatment was 7.1 days (Ciprodex and Ciloxan) or 7.0 days (Cortisporin). For each drug, the median duration of treatment was 7 days with a range of 1 to 14 days.

7.1.1.1.2. Adverse Events

7.1.1.1.2.1. All Adverse Events

Table 35 shows adverse events occurring in ≥1% of any treatment group during the study period. Adverse events were reported in 121 patients receiving Ciprodex (39.7%), 114 receiving Ciloxan (37.4%), and 115 receiving Cortisporin (38.5%).

Table 35: Adverse Events Occurring in ≥1% of Any Treatment Group

	Ciprodex (N=305)		Ciloxan (N=305)		Cortisporin (N=299)	
	n	(%)	*n*	(%)	*n*	(%)
Otic						
Otitis media	15	(4.9)	9	(3.0)	7	(2.3)
Otitis externa (nonstudy ear)	12	(3.9)	11	(3.6)	18	(6.0)
Pruritis, ear	6	(2.0)	8	(2.6)	7	(2.3)
Ear congestion	5	(1.6)	4	(1.3)	4	(1.3)
Pain, ear	4	(1.3)	4	(1.3)	5	(1.7)
Injury, accidental	3	(1.0)	2	(0.7)	-	-
Discomfort, ear	2	(0.7)	-	-	3	(1.0)
Nonotic						
Body as a whole						
Headache	24	(7.9)	26	(8.5)	29	(9.7)
Pain	9	(3.0)	6	(2.0)	4	(1.3)
Infection	6	(2.0)	7	(2.3)	9	(3.0)
Injury, accidental	4	(1.3)	5	(1.6)	1	(0.3)
Pain, abdomen	4	(1.3)	3	(1.0)	5	(1.7)
Allergy	3	(1.0)	1	(0.3)	4	(1.3)
Cold syndrome	3	(1.0)	5	(1.6)	4	(1.3)
Flu syndrome	3	(1.0)	1	(0.3)	2	(0.7)
Surgical/medical procedure	3	(1.0)	3	(1.0)	-	-
Fever	2	(0.7)	3	(1.0)	4	(1.3)
Digestive system						
Diarrhea	8	(2.6)	-	-	4	(1.3)
Nausea	5	(1.6)	3	(1.0)	6	(2.0)
Vomiting	4	(1.3)	4	(1.3)	4	(1.3)
Dyspepsia	1	(0.3)	3	(1.0)	1	(0.3)
Musculoskeletal system						
Bone fracture, spontaneous	-	-	1	(0.3)	3	(1.0)
Respiratory system						
Rhinitis	14	(4.6)	8	(2.6)	9	(3.0)
Pharyngitis	8	(2.6)	9	(3.0)	9	(3.0)
Cough, increased	6	(2.0)	1	(0.3)	3	(1.0)
Skin and appendages						
Erythema	3	(1.0)	-	-	1	(0.3)
Skin disorder	3	(1.0)	1	(0.3)	-	-
Dermatitis	1	(0.3)	3	(1.0)	3	(1.0)

Adapted from C-98-18 study report, Volume 17, Table 14.3.1.5-1

The most frequently reported adverse events in patients receiving Ciprodex were headache (7.9%), otitis media (4.9%), rhinitis (4.6%), otitis externa in the nonstudy ear (3.9%), nonotic pain (3.0%), pharyngitis (2.6%), and diarrhea (2.6%). For all study groups, the reported adverse events were considered by investigators to be nonserious and generally mild to moderate in intensity.

Comment: The adverse event profiles were generally similar across study groups. Most of the reported nonotic adverse events are unlikely to be related to a topical

study therapy. Attribution of causality is more difficult for the otic adverse events. Otitis media and otitis externa in the nonstudy ear are not related to study therapy. Events such as ear pruritis and ear pain, however, could be related to study therapy but are also common manifestations of AOE.

7.1.1.1.2.2. Treatment-Related Adverse Events

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 36.

Table 36. Treatment-Related Adverse Events

	Ciprodex (N=305)		Ciloxan (N=305)		Cortisporin (N=299)	
	n	(%)	n	(%)	n	(%)
Otic						
Pruritis, ear	5	(1.6)	4	(1.3)	4	(1.3)
Discomfort, ear	1	(0.3)			3	(1.0)
Hearing decreased	1	(0.3)			1	(0.3)
Ear debris	1	(0.3)				
Ear congestion			1	(0.3)		
Ear disorder					1	(0.3)
Pain, ear					1	(0.3)
Nonotic						
Body as a whole						
Headache			1	(0.3)		
Digestive system						
Nausea					1	(0.3)
Skin and appendages						
Erythema	2	(0.7)				
Dermatitis			1	(0.3)	1	(0.3)

Adapted from C-98-18 study report, Volume 17, Table 14.3.1.6-1

The most common treatment-related adverse event in all study groups was ear pruritis, which was reported in 1.3% to 1.6% of patients. The reports of erythema in the Ciprodex group were for facial flushing in one patient and "slight reddish rash by right ear" in another. All of the reported treatment-related adverse events were considered to be mild to moderate in intensity with the exception of severe ear discomfort (burning) in one Cortisporin patient.

7.1.1.1.2.3. Discontinuations Due to Adverse Events

Thirty-seven (4.1%) of the 909 patients enrolled were discontinued from the study because of adverse events: 14 Ciprodex patients (4.6%), 13 Ciloxan patients (4.3%), and 10 Cortisporin patients (3.3%). The most frequently reported adverse event that resulted in discontinuation from the study was otitis media. No patients were discontinued from the study because of treatment-related adverse events.

7.1.1.1.2.4. Serious Adverse Events

No serious adverse events were reported in this study.

7.1.1.1.2.5. Deaths

No deaths were reported in this study.

7.1.1.1.3. Conclusions

In this study, Ciprodex was well-tolerated and had an adverse event profile similar to that of the approved comparator, Cortisporin. The most frequently reported adverse events in patients receiving Ciprodex were headache, otitis media, rhinitis, otitis externa in the nonstudy ear, nonotic pain, pharyngitis, and diarrhea. The most frequently reported adverse event attributed to Ciprodex was ear pruritis. No patients were discontinued from the study because of a treatment-related adverse event. No serious adverse events were reported.

7.1.1.2. Protocol C-98-19: "Topical CILODEX (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to CORTISPORIN® Suspension (Neomycin 0.35%, Polymyxin 10,000 IU/mL, Hydrocortisone 1.0%) for Treatment of Patients with Acute Otitis Externa (AOE)"

7.1.1.2.1. Extent of Exposure

In this study, 232 patients received Ciprodex and 236 patients received Cortisporin. For each drug, the mean duration of treatment was 7.1 days, and the median duration was 7 days. Treatment ranged from 1 to 15 days for Ciprodex and from 1 to 12 days for Cortisporin.

7.1.1.2.2. Adverse Events

7.1.1.2.2.1. All Adverse Events

Table 37 shows adverse events occurring in ≥1% of any treatment group during the study period. Adverse events were reported in 89 patients receiving Ciprodex (38.4%) and in 96 receiving Cortisporin (40.7%).

Table 37. Adverse Events Occurring in ≥1% of Any Treatment Group

	Ciprodex (N=232)		Cortisporin (N=236)	
	n	(%)	n	(%)
Otic				
Otitis externa (nonstudy ear)	7	(3.0)	8	(3.4)
Ear debris	6	(2.6)	2	(0.8)
Pain, ear	6	(2.6)	5	(2.1)
Otitis media	5	(2.2)	7	(3.0)
Pruritis, ear	5	(2.2)	16	(6.8)
Ear congestion	4	(1.7)	9	(3.8)
Infection, superimposed ear	3	(1.3)	-	-
Ear disorder	2	(0.9)	4	(1.7)
Discomfort, ear	1	(0.4)	3	(1.3)
Eardrum perforation	1	(0.4)	3	(1.3)
Hemorrhage, ear	1	(0.4)	3	(1.3)
Nonotic				
Body as a whole				
Headache	21	(9.1)	14	(5.9)
Pain	3	(1.3)	5	(2.1)
Infection	2	(0.9)	4	(1.7)
Flu syndrome	1	(0.4)	3	(1.3)
Digestive system				
Vomiting	3	(1.3)	1	(0.4)
Dyspepsia	-	-	3	(1.3)
Respiratory system				
Rhinitis	8	(3.4)	8	(3.4)
Cough, increased	7	(3.0)	6	(2.5)
Pharyngitis	5	(2.2)	8	(3.4)

Adapted from C-98-19 study report, Volume 12, Table 14.3.1.5-1

The most frequently reported adverse events in patients receiving Ciprodex were headache (9.1%), rhinitis (3.4%), otitis externa in the nonstudy ear (3.4%), increased cough (3.0%), ear debris (2.6%), ear pain (2.6%), otitis media (2.2%), ear pruritis (2.2%), and pharyngitis (2.2%). Except for a single report of prostate cancer in an elderly Cortisporin patient, the reported adverse events were considered by investigators to be nonserious and generally mild to moderate in intensity.

Comment: In this study, headache was reported more frequently in Ciprodex patients, and ear pruritis was reported more frequently in Cortisporin patients. The adverse event profiles were otherwise generally similar between groups and similar to the reports from C-98-18.

7.1.1.2.2.2. Treatment-Related Adverse Events

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 38.

Table 38. Treatment-Related Adverse Events

	Ciprodex (N=232)		Cortisporin (N=236)	
	n	(%)	n	(%)
Otic				
Pruritis, ear	3	(1.3)	11	(4.7)
Ear congestion	2	(0.9)	4	(1.7)
Ear debris	2	(0.9)	2	(0.8)
Infection, superimposed ear	3	(1.3)		
Ear disorder	1	(0.4)	1	(0.4)
Pain, ear	2	(0.9)		
Discomfort, ear			3	(1.3)
Hearing, decreased			2	(0.8)
Erythema, canal			1	(0.4)
Nonotic				
None				

Adapted from C-98-19 study report, Volume 12, Table 14.3.1.6-1

The most frequently reported treatment-related adverse events in Ciprodex patients were ear pruritis (1.3%) and superimposed ear infection (1.3%). The most frequently reported treatment-related adverse events in Cortisporin patients were ear pruritis (4.7%), ear congestion (1.7%), and ear discomfort (1.3%). All of the reported treatment-related adverse events were considered to be mild to moderate in intensity.

Comment: Ear pruritis was reported more commonly in Cortisporin patients in this study. No nonotic treatment-related adverse events were reported. The findings are otherwise similar to those reported in C-98-18.

7.1.1.2.2.3. Discontinuations Due to Adverse Events

Seventeen (3.6%) of the 468 patients enrolled were discontinued from the study because of adverse events: 6 Ciprodex patients (2.6%) and 11 Cortisporin patients (4.7%). The most frequently reported adverse event that resulted in discontinuation from the study was otitis media. Two Ciprodex patients were discontinued from the study because of treatment-related adverse events; both developed fungal superinfections. No Cortisporin patients were discontinued from the study because of treatment-related adverse events.

7.1.1.2.2.4. Serious Adverse Events

No serious adverse events were reported in Ciprodex patients. A 79 year old Cortisporin patient was diagnosed with prostate cancer following Cortisporin treatment. This event was determined to be unrelated to study drug treatment.

7.1.1.2.2.5. Deaths

No deaths were reported in this study.

7.1.1.2.3. Conclusions

In this study, Ciprodex was well-tolerated and had an adverse event profile similar to that of the approved comparator, Cortisporin. The most frequently reported adverse events in patients receiving Ciprodex were headache, rhinitis, otitis externa in the nonstudy ear, increased cough, ear debris, ear pain, otitis media, ear pruritis, and pharyngitis. The most frequently reported adverse events attributed to Ciprodex were ear pruritis and superimposed ear infection. Two Ciprodex patients were discontinued from the study because of fungal superinfections. No serious adverse events were reported in Ciprodex patients.

7.1.2. Acute Otitis Media in Patients with Tympanostomy Tubes

7.1.2.1. Protocol C-99-59: "Safety and Efficacy of Topical CIPRODEX® (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to CILOXAN® (Ciprofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT)"

7.1.2.1.1. Extent of Exposure

In this study, 103 patients received Ciprodex and 98 patients received Ciloxan. The mean duration of treatment was 6.7 days for Ciprodex and 6.4 days for Ciloxan; median duration was 7 days for each study drug. Treatment ranged from 1 to 11 days for Ciprodex and from 1 to 12 days for Ciloxan.

7.1.2.1.2. Adverse Events

7.1.2.1.2.1. All Adverse Events

Table 39 shows adverse events occurring in ≥1% of any treatment group during the study period. Adverse events were reported in 49 patients receiving Ciprodex (47.6%) and in 51 receiving Ciloxan (52.0%).

Comment: Adverse events were reported more commonly in patients with AOMT than in those with AOE.

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Table 39. Adverse Events Occurring in ≥1% of Any Treatment Group

	Ciprodex (N=103)		Ciloxan (N=98)	
	n	(%)	n	(%)
Otic				
Pain, ear	5	(4.9)	8	(8.2)
Otitis media (nonstudy ear)	4	(3.9)	9	(9.2)
Discomfort, ear	2	(1.9)	1	(1.0)
Ear disorder	2	(1.9)	2	(2.0)
Discharge, ear	1	(1.0)	1	(1.0)
Otitis externa	1	(1.0)	-	-
Pruritis, ear	1	(1.0)	1	(1.0)
Precipitate, ear	-	-	3	(3.1)
Nonotic				
Body as a whole				
Fever	11	(10.7)	7	(7.1)
Infection	7	(6.8)	7	(7.1)
Pain	3	(2.9)	3	(3.1)
Injury, Accidental	1	(1.0)	2	(2.0)
Cold syndrome	2	(1.9)	-	-
Flu syndrome	1	(1.0)	1	(1.0)
Headache	1	(1.0)	1	(1.0)
Pain, abdominal	1	(1.0)	-	-
Asthenia	-	-	1	(1.0)
Digestive system				
Diarrhea	1	(1.0)	3	(3.1)
Vomiting	2	(1.9)	-	-
Nervous system				
Irritability	2	(1.9)	5	(5.1)
Crying	1	(1.0)	1	(1.0)
Respiratory system				
Rhinitis	8	(7.8)	7	(7.1)
Cough, increased	6	(5.8)	3	(3.1)
Bronchitis	1	(1.0)	2	(2.0)
Sinusitis	2	(1.9)	1	(1.0)
Asthma	-	-	3	(3.1)
Pharyngitis	-	-	3	(3.1)
Lung Disorder	-	-	1	(1.0)
Pneumonia	-	-	1	(1.0)
Skin and appendages				
Pruritis	1	(1.0)	2	(2.0)
Dermatitis	1	(1.0)	1	(1.0)
Erythema	-	-	1	(1.0)
Special senses				
Taste perversion	3	(2.9)	-	-
Lid margin, crusting	-	-	1	(1.0)
Urogenital system				
Infection, urinary tract	1	(1.0)	-	-

Adapted from C-99-59 study report, Volume 3, Table 14.3.1.5-1

The most frequently reported adverse events in patients receiving Ciprodex were fever (10.7%), rhinitis (7.8%), infection (primarily upper respiratory, 6.8%), increased cough (5.8%), ear pain (4.9%), otitis media in the nonstudy ear (3.9%), taste perversion (2.9%), and nonotic pain (2.9%). Except for a single report of pneumonia in a Ciloxan patient, the reported adverse events were considered by investigators to be nonserious and generally mild to moderate in intensity.

Comment: The nonotic adverse events in AOMT patients include many of the manifestations of associated viral respiratory infections.

7.1.2.1.2.2. Treatment-Related Adverse Events

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 40.

Table 40. Treatment-Related Adverse Events

	Ciprodex (N=103)		Ciloxan (N=98)	
	n	(%)	n	(%)
Otic				
Discomfort, ear	2	(1.9)	1	(1.0)
Pain, ear	2	(1.9)	1	(1.0)
Pruritis, ear	1	(1.0)	1	(1.0)
Precipitate, ear			3	(3.1)
Nonotic				
Nervous system				
Crying	1	(1.0)	1	(1.0)
Special senses				
Taste perversion	1	(1.0)		

Adapted from C-99-59 study report, Volume 3, Table 14.3.1.6-1

The most frequently reported treatment-related adverse events in patients receiving Ciprodex were ear discomfort (1.9%) and ear pain (1.9%). The most frequently reported treatment-related adverse event in patients receiving Ciloxan was ear precipitate (3.1%).

7.1.2.1.2.3. Discontinuations Due to Adverse Events

Nineteen (9.5%) of the 201 patients enrolled were discontinued from the study because of adverse events: 7 Ciprodex patients (6.8%) and 12 Ciloxan patients (12.2%). The most frequently reported adverse event that resulted in discontinuation from the study was otitis media in the nonstudy ear. No Ciprodex patients were discontinued from the study because of treatment-related adverse events. One Ciloxan patient was discontinued because of crying that was attributed to study treatment.

7.1.2.1.2.4. Serious Adverse Events

No serious adverse events were reported in Ciprodex patients. A 1 year old Ciloxan patient was hospitalized with pneumonia on study day 8. The patient responded well to therapy. This event was determined to be unrelated to study drug treatment.

7.1.2.1.2.5. Deaths

No deaths were reported in this study.

7.1.2.1.3. Audiometry

Audiometric examinations, including determination of speech reception threshold and bone and air conduction audiometry, were performed at study entry and exit in patients 4 to 12 years of age. Speech reception thresholds were determined in 38 patients, 23 who received Ciprodex and 15 who received Ciloxan. Speech reception thresholds improved by a mean of 12.4 dB in the Ciprodex patients and 9.0 dB in the Ciloxan patients; the difference between groups was not significant (p=0.3038). Bone and air conduction audiometry was performed in 40 patients, 24 who received Ciprodex and 16 who received Ciloxan. No patient in either group had a clinically relevant hearing decrease from baseline.

7.1.2.1.4. Conclusions

In this study, the most frequently reported adverse events in patients receiving Ciprodex were fever, rhinitis, infection (primarily upper respiratory), increased cough, ear pain, otitis media in the nonstudy ear, taste perversion, and nonotic pain. The most frequently reported adverse events attributed to Ciprodex were ear discomfort and ear pain. No Ciprodex patients were discontinued from the study because of treatment-related adverse events. One Ciloxan patient was discontinued because of crying that was attributed to study treatment. One Ciloxan patient was hospitalized because of a serious adverse event (pneumonia) that was determined to be unrelated to study treatment. Speech reception thresholds improved in both groups.

7.1.2.2. Protocol C-00-52: "Safety and Efficacy of Topical CIPRODEX Otic (Ciprofloxacin 0.3%, Dexamethasone 0.1%) Suspension Compared to FLOXIN® Otic (Ofloxacin 0.3%) Solution in the Treatment of Acute Otitis Media with Tympanostomy Tubes (AOMT)"

7.1.2.2.1. Extent of Exposure

In this study, 297 patients received Ciprodex and 302 patients received ofloxacin. The mean and median durations of treatment with Ciprodex were 6.7 days and 7 days, respectively, with a range of 1 to 11 days. The mean and median durations of treatment with ofloxacin were 9.0 days and 10 days, respectively, with a range of 1 to 18 days.

7.1.2.2.2. Adverse Events

7.1.2.2.2.1. All Adverse Events

Table 41 shows adverse events occurring in ≥1% of any treatment group during the study period. Adverse events were reported in 137 patients receiving Ciprodex (46.1%) and in 165 receiving ofloxacin (54.6%).

Table 41. Adverse Events Occurring in ≥1% of Any Treatment Group

	Ciprodex (N=297)		Ofloxacin (N=302)	
	n	(%)	n	(%)
Otic				
Otitis media (nonstudy ear)	25	(8.4)	35	(11.6)
Pain, ear	17	(5.7)	18	(6.0)
Discomfort, ear	10	(3.4)	6	(2.0)
Device extrusion	7	(2.4)	9	(3.0)
Discharge, ear	7	(2.4)	8	(2.6)
Device blockage	6	(2.0)	7	(2.3)
Ear debris	3	(1.0)	6	(2.0)
Precipitate, ear	2	(0.7)	3	(1.0)
Pruritis, ear	1	(0.3)	3	(1.0)
Nonotic				
Body as a whole				
Fever	23	(7.7)	28	(9.3)
Infection	11	(3.7)	13	(4.3)
Pain	7	(2.4)	4	(1.3)
Cold syndrome	5	(1.7)	7	(2.3)
Pain, abdomen	4	(1.3)	4	(1.3)
Flu syndrome	2	(0.7)	3	(1.0)
Headache	2	(0.7)	5	(1.7)
Digestive system				
Vomiting	7	(2.4)	9	(3.0)
Diarrhea	6	(2.0)	9	(3.0)
Monilia, oral	3	(1.0)	1	(0.3)
Nervous system				
Irritability	5	(1.7)	7	(2.3)
Respiratory system				
Rhinitis	17	(5.7)	15	(5.0)
Cough, increased	6	(2.0)	15	(5.0)
Pharyngitis	5	(1.7)	6	(2.0)
Asthma	1	(0.3)	3	(1.0)
Pneumonia	-	-	3	(1.0)
Skin and appendages				
Dermatitis	2	(0.7)	4	(1.3)
Special senses				
Conjunctivitis	4	(1.3)	2	(0.7)
Taste perversion	1	(0.3)	3	(1.0)

Adapted from C-00-52 study report, Volume 7, Table 14.3.1.5-1

The most frequently reported adverse events in patients receiving Ciprodex were otitis media in the nonstudy ear (8.4%), fever (7.7%), ear pain (5.7%), rhinitis (5.7%), infection (upper respiratory, 3.7%), ear discomfort (3.4%), device extrusion (2.4%), ear discharge (2.4%), nonotic pain (2.4%), vomiting (2.4%), device blockage (2.0%), diarrhea (2.0%), and increased cough (2.0%).

7.1.2.2.2.2. Treatment-Related Adverse Events

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 42.

Table 42. Treatment-Related Adverse Events

	Ciprodex (N=297)		Ofloxacin (N=302)	
	n	(%)	n	(%)
Otic				
Pain, ear	7	(2.4)	9	(3.0)
Discomfort, ear	10	(3.4)	3	(1.0)
Precipitate, ear	2	(0.7)	3	(1.0)
Device blockage	1	(0.3)		
Tinnitus	1	(0.3)		
Infection, superimposed ear			2	(0.7)
Irritation, ear			2	(0.7)
Pruritis, ear			2	(0.7)
Ear debris			1	(0.3)
Edema, eardrum			1	(0.3)
Hyperemia, eardrum			1	(0.3)
Nonotic				
Body as a whole				
Headache			1	(0.3)
Digestive system				
Monilia, oral	1	(0.3)	1	(0.3)
Diarrhea			1	(0.3)
Nervous system				
Irritability	2	(0.7)		
Dizziness	1	(0.3)		
Crying			1	(0.3)
Respiratory system				
Cough, increased			1	(0.3)
Skin and appendages				
Erythema	1	(0.3)		
Special senses				
Taste perversion	1	(0.3)	3	(1.0)

Adapted from C-00-52 study report, Volume 7, Table 14.3.1.6-1

The most frequently reported treatment-related adverse events in Ciprodex patients were ear discomfort (3.4%) and ear pain (2.4%). All of the treatment-related adverse events were considered to be nonserious and mild to moderate in intensity.

7.1.2.2.2.3. Discontinuations Due to Adverse Events

Seventy-eight (13.0%) of the 599 patients enrolled were discontinued from the study because of adverse events: 32 Ciprodex patients (10.4%) and 46 ofloxacin patients (15.2%). The most frequently reported adverse event that resulted in discontinuation from the study was otitis media in the nonstudy ear, which occurred in 19 Ciprodex patients and 26 ofloxacin patients. Two discontinuations were due to treatment-related adverse events: one Ciprodex patient was discontinued because of ear discomfort (burning), and one ofloxacin patient was discontinued because of ear irritation.

Comment: The incidence of discontinuations was greater in the ofloxacin group. The incidence of all adverse events was also somewhat greater (54.6% vs. 46.1%), as was the incidence of treatment-related adverse events (10.6% vs. 9.1%). Exposure to ofloxacin was for 10 days vs. 7 days for Ciprodex.

7.1.2.2.2.4. Serious Adverse Events

Three serious adverse events were reported in this study. An 11 month old Ciprodex patient was hospitalized for 4 days for severe abdominal pain that began following the completion of study therapy but before the test of cure visit. The pain resolved with antacid treatment, and the patient completed the study. A 1 year old ofloxacin patient was hospitalized with severe pneumonia following the completion of study therapy but before the test of cure visit. The pneumonia resolved with antimicrobial therapy, and the patient completed the study. Another 1 year old ofloxacin patient was hospitalized for 5 days for cellulitis of the left foot following an insect bite. This patient was discontinued from the study. These events were determined by the investigators and medical monitor to be unrelated to study drug treatment.

7.1.2.2.2.5. Deaths

No deaths were reported in this study.

7.1.2.2.3. Audiometry

Audiometric examinations, including determination of speech reception threshold and bone and air conduction audiometry, were performed at study entry and exit in patients 4 to 12 years of age. Speech reception thresholds were determined in 86 patients, 46 who received Ciprodex and 40 who received ofloxacin. Speech reception thresholds improved by a mean of 7.8 dB in the Ciprodex patients and 10.0 dB in the ofloxacin patients; the difference between groups was not significant ($p=0.3863$). Bone and air conduction audiometry was performed in 92 patients, 47 who received Ciprodex and 45 who received ofloxacin. One Ciprodex patient had a decrease in hearing from baseline at the

test of cure visit but had no clinically relevant hearing decrease at follow-up 7 weeks later. At the test of cure visit, this child was noted to be ill and uncooperative with testing, and the audiometry results were reported to be inconsistent. No patient in either group had a clinically relevant hearing decrease from baseline.

7.1.2.2.4. Conclusions

In this study, the most frequently reported adverse events in patients receiving Ciprodex were otitis media in the nonstudy ear, fever, ear pain, rhinitis, upper respiratory infection, ear discomfort, device extrusion, ear discharge, nonotic pain, vomiting, device blockage, diarrhea, and increased cough. The most frequently reported adverse events attributed to Ciprodex were ear discomfort and ear pain. One Ciprodex patient was discontinued from the study because of ear discomfort (burning) that was attributed to study treatment. One ofloxacin patient was discontinued because of ear irritation that was attributed to study treatment. One Ciloxan patient was hospitalized because of a serious adverse event (abdominal pain) that was determined to be unrelated to study treatment. Two ofloxacin patients were hospitalized because of serious adverse events (pneumonia, cellulitis) that were determined to be unrelated to study treatment. Speech reception thresholds improved in both groups.

7.2. Integrated Summary of Safety

7.2.1. Extent of Exposure

7.2.1.1. Phase 1 Studies

The applicant performed three phase 1 studies: a skin sensitization study, C-97-56, and two pharmacokinetic studies in patients undergoing tympanostomy tube insertion, C-00-68 and C-02-58. Protocol C-02-58 was performed to obtain additional data to supplement the data that the FDA considered valid from C-00-68. The clinical and safety evaluations for these protocols were identical. Therefore, in this review, the data from these two studies are combined.

Table 43 shows the numbers of subjects exposed to study drug in the phase 1 studies.

Table 43. Exposure to Study Drugs in Phase 1 Studies

Protocol	Ciprodex skin	Ciloxan skin	Maxidex skin	Saline skin	Ciprodex otic	Total
Skin sensitization C-97-56	231	114	114	115		574
Pharmacokinetics: AOMT C-00-68/C-02-58					11	11
Total	**231**	**114**	**114**	**115**	**11**	**585**

Adapted from Summary of Clinical Safety, Module 2, Volume 2, Table 2.7.4.1.1-1

Table 44 shows the duration of exposure to study drug in the skin sensitization study. Participants in this study were to receive nine applications of a topical patch over a 21-

day induction period, followed by a 2-week rest period, and then a 48-hour challenge application at another site.

Table 44. Duration of Exposure in Skin Sensitization Study (C-97-56)

Test article	Induction <9 applications; no challenge	Induction=9 applications; no challenge	Induction=9 applications; 1 challenge	Total
Ciprodex skin	16	4	211	231
Ciloxan skin	11	5	98	114
Maxidex skin	7	1	106	114
Saline skin	9	-	106	115
Total	**43**	**10**	**521**	**574**

Adapted from Summary of Clinical Safety, Module 2, Volume 2, Table 2.7.4.1.2.3-1

The 11 participants in the pharmacokinetic studies received a single otic dose of Ciprodex.

7.2.1.2. Phase 2 and 3 Studies

The applicant performed two efficacy and safety studies for the AOE indication (C-98-18 and C-98-19) and two studies for the AOMT indication (C-99-59 and C-00-52). Table 45 shows the numbers of patients exposed to study drug in these studies. In the AOE studies, 537 of the 1377 patients enrolled received Ciprodex. In the AOMT studies, 400 of the 800 patients enrolled received Ciprodex.

Table 45. Exposure to Study Drugs in Phase 2 and 3 Studies

Protocol	Ciprodex	Ciloxan	Cortisporin	Ofloxacin	Total
AOE studies					
C-98-18	305	305	299		909
C-98-19	232		236		468
Subtotal	**537**	**305**	**535**		**1377**
AOMT studies					
C-99-59	103	98			201
C-00-52	297			302	599
Subtotal	**400**	**98**			**800**
Total	**937**	**403**	**535**	**302**	**2177**

Adapted from Summary of Clinical Safety, Module 2, Volume 2, Table 2.7.4.1.1-1

Table 46 shows the duration of exposure to study drugs in the phase 2 and 3 studies. All study drugs were prescribed for 7 days in the AOE studies. In the AOMT studies, Ciprodex and Ciloxan were prescribed for 7 days, and ofloxacin was prescribed for 10 days. In all studies, the mean and median durations of exposure to each study drug were within 1 day of the prescribed duration.

Table 46. Duration of Exposure to Study Drugs in Phase 2 and 3 Studies

Treatment	Duration				Total
AOE studies	**1-3 Days**	**4-7 Days**	**>7 Days**		
Ciprodex	22	374	141		537
Ciloxan	14	223	68		305
Cortisporin	22	371	142		535
Total	**58**	**968**	**351**		**1377**
AOMT studies	**1-3 Days**	**4-7 Days**	**8-10 Days**	**>10 Days**	
Ciprodex	23	360	14	3	400
Ciloxan	12	74	11	1	98
Ofloxacin	21	33	234	14	302
Total	**56**	**467**	**259**	**18**	**800**

Adapted from Summary of Clinical Safety, Module 2, Volume 2, Tables 2.7.4.1.2.1-1 and 2.7.4.1.2.2-1

7.2.2. Demographics

7.2.2.1. Phase 1 Studies

Table 47 shows the baseline characteristics of subjects enrolled in the phase 1 studies. The skin sensitization study enrolled only healthy adults, while the AOMT pharmacokinetic studies enrolled pediatric patients who were undergoing tympanostomy tube placement.

Table 47. Baseline Subject Characteristics: Phase 1 Studies

	Skin sensitization										AOMT PK	
	Ciprodex (N=231)		Ciloxan (N=114)		Maxidex (N=114)		Saline (N=115)		Total (N=574)		Ciprodex (N=11)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Age (years)												
<2											3	(27)
2-11											7	(64)
12-17											1	(9)
18-64	192	(83)	98	(86)	90	(79)	88	(77)	468	(82)		
65-74	28	(12)	9	(8)	20	(18)	19	(17)	76	(13)		
≥75	11	(5)	7	(6)	4	(4)	8	(7)	30	(5)		
Sex												
Male	55	(24)	34	(30)	30	(26)	31	(27)	150	(26)	9	(82)
Female	176	(76)	80	(70)	84	(74)	84	(73)	424	(74)	2	(18)
Race												
White	211	(91)	105	(92)	109	(96)	101	(88)	526	(92)	8	(73)
Black	13	(6)	4	(4)	2	(2)	9	(8)	28	(5)	1	(9)
Other	7	(3)	5	(5)	3	(3)	5	(4)	20	(3)	2	(18)

Adapted from Summary of Clinical Safety, Module 2, Volume 3, Table 2.7.4.7.2-3 and 3/31/03 submission, Table 10.4-1

Comment: There is a striking female predominance in enrollment in the skin sensitization study. There appear to be no significant demographic differences among treatment groups. There was limited enrollment in the pharmacokinetic studies.

7.2.2.2. Phase 2 and 3 Studies

Table 48 shows the baseline characteristics of patients enrolled in the phase 2 and 3 studies. The AOE studies enrolled patients one year of age and older, while the AOMT studies enrolled only pediatric patients ages 6 months to 12 years. Demographic data are therefore presented by indication.

Table 48. Baseline Patient Characteristics: Phase 2 and 3 Studies

AOE studies								
	Ciprodex (N=537)		**Ciloxan (N=305)**		**Cortisporin (N=535)**		**Total (N=1377)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
12-23 months	3	(0.6)	2	(0.7)	2	(0.4)	7	(0.5)
2-11 years	202	(37.6)	137	(44.9)	208	(38.9)	547	(39.7)
12-17 years	111	(20.7)	54	(17.7)	106	(19.8)	271	(19.7)
18-64 years	211	(39.3)	102	(33.4)	205	(38.3)	518	(37.6)
65-74 years	6	(1.1)	5	(1.6)	8	(1.5)	19	(1.4)
≥75 years	4	(0.7)	5	(1.6)	6	(1.1)	15	(1.1)
Sex								
Male	265	(49.3)	126	(41.3)	249	(46.5)	640	(46.5)
Female	272	(50.7)	179	(58.7)	286	(53.5)	737	(53.5)
Race								
White	476	(88.6)	259	(84.9)	454	(84.9)	1189	(86.3)
Black	19	(3.5)	16	(5.2)	24	(4.5)	59	(4.3)
Asian	8	(1.5)	1	(0.3)	12	(2.2)	21	(1.5)
Other	34	(6.3)	29	(9.5)	45	(8.4)	108	(7.8)
AOMT studies								
	Ciprodex (N=400)		**Ciloxan (N=98)**		**Ofloxacin (N=302)**		**Total (N=800)**	
	n	(%)	n	(%)	n	(%)	n	(%)
Age								
6-23 months	195	(48.8)	52	(53.1)	148	(49.0)	395	(49.4)
2-11 years	200	(50.0)	46	(46.9)	154	(51.0)	400	(50.0)
12-17 years	5	(1.3)	-	-	-	-	5	(0.6)
Sex								
Male	231	(57.8)	53	(54.1)	201	(66.6)	485	(60.6)
Female	169	(42.3)	45	(45.9)	101	(33.4)	315	(39.4)
Race								
White	327	(81.8)	78	(79.6)	244	(80.8)	649	(81.1)
Black	24	(6.0)	8	(8.2)	17	(5.6)	49	(6.1)
Asian	-	-	-	-	3	(1.0)	3	(0.4)
Hispanic	26	(6.5)	-	-	28	(9.3)	54	(6.8)
Other	23	(5.8)	12	(12.2)	10	(3.3)	45	(5.6)

Adapted from Summary of Clinical Safety, Module 2, Volume 3, Tables 2.7.4.7.2-2 and 2.7.4.7.2-1

Comment: The demographic characteristics of the study populations comprising the safety database adequately reflect those of the target populations for each indication. There appear to be no clinically significant differences among the treatment groups for each indication.

7.2.3. Adverse Events

7.2.3.1. All Adverse Events

7.2.3.1.1. Phase 1 Studies

Table 49 shows adverse events occurring in >1% of any treatment group in the skin sensitization study.

Table 49. Adverse Events Occurring in >1% of Any Group: Skin Sensitization Study

	Ciprodex (N=231)		Ciloxan (N=114)		Maxidex (N=114)		Saline (N=115)	
	n	(%)	n	(%)	n	(%)	n	(%)
Body as a whole								
Headache	24	(10.4)	11	(9.6)	21	(18.4)	13	(11.3)
Pain	7	(3.0)	3	(2.6)	1	(0.9)	-	-
Cold syndrome	4	(1.7)	2	(1.8)	-	-	1	(0.9)
Pain, back	3	(1.3)	1	(0.9)	2	(1.8)	1	(0.9)
Flu syndrome	2	(0.9)	2	(1.8)	-	-	-	-
Injury, accidental	1	(0.4)	-	-	2	(1.8)	-	-
Surgical/medical procedure	-	-	2	(1.8)	-	-	5	(4.3)
Digestive system								
Dyspepsia	6	(2.6)	-	-	2	(1.8)	2	(1.7)
Nausea	4	(1.7)	1	(0.9)	2	(1.8)	1	(0.9)
Musculoskeletal system								
Myalgia	1	(0.4)	-	-	4	(3.5)	2	(1.7)
Respiratory system								
Rhinitis	12	(5.2)	1	(0.9)	3	(2.6)	2	(1.7)
Cough, increased	4	(1.7)	-	-	2	(1.8)	-	-
Pharyngitis	3	(1.3)	-	-	1	(0.9)	-	-
Urogenital system								
Dysmenorrhea	6	(2.6)	-	-	1	(0.9)	2	(1.7)
Infection, urinary tract	4	(1.7)	-	-	-	-	1	(0.9)

Adapted from Summary of Clinical Safety, Module 2, Volume 3, Table 2.7.4.7.3-2

The most frequently reported adverse event in each group was headache. The reported adverse events were generally considered by investigators to be mild to moderate in intensity.

Comment: The adverse event profiles were generally similar across study groups, including the saline placebo group. These events are not likely to be related to topical drug administration. There were seven cutaneous adverse reactions reported in six subjects: allergic reaction ("tape reaction") in a Ciprodex subject, single reports of acne and allergic reaction ("tape reaction") in two Cilodex subjects, photosensitivity ("sunburn on back area") in a Maxidex subject, and reports of dermatitis and skin discoloration ("rash and bluish discoloration over entire body") in one saline subject and urticaria ("hives (swelling and rash) around eyes, nose, and neck area") in another. These events are also unlikely to be related to topical study drug administration.

In the AOMT pharmacokinetic studies, seven adverse events were reported in four patients who received Ciprodex: one with pain, vomiting, and irritability; one with pain and vomiting, one with pain only, and one with pharyngitis. These events were considered by the investigator to be nonserious and mild to moderate in intensity.

Comment: The significance of these events in patients in the immediate postoperative period is unclear. They are unlikely to be related to a single otic dose of Ciprodex.

7.2.3.1.2. Phase 2 and 3 Studies

Comment: For the phase 2 and 3 studies, adverse event summaries are presented by indication. The adverse event profiles are somewhat different for each indication, and the proposed and recommended labeling lists adverse events by indication. The labeling for ofloxacin otic solution, which has similar indications, lists adverse events by indication.

7.2.3.1.2.1. Acute Otitis Externa

Table 50 shows adverse events occurring in >1% of treatment group in the pooled AOE studies. Adverse events were reported in 210 of 537 Ciprodex patients (39.1%), 114 of 305 Ciloxan patients (37.4%), and 211 of 535 Cortisporin patients (39.4%).

Table 50. Adverse Events Occurring in ≥1% of Any Group: Pooled AOE Studies

	Ciprodex (N=537)		Ciloxan (N=305)		Cortisporin (N=535)	
	n	(%)	n	(%)	n	(%)
Otic						
Otitis media	20	(3.7)	9	(3.0)	14	(2.6)
Otitis externa (nonstudy ear)	19	(3.5)	11	(3.6)	26	(4.9)
Pruritis, ear	11	(2.0)	8	(2.6)	23	(4.3)
Pain, ear	10	(1.9)	4	(1.3)	10	(1.9)
Ear congestion	9	(1.7)	4	(1.3)	13	(2.4)
Ear debris	8	(1.5)	1	(0.3)	3	(0.6)
Discomfort, ear	3	(0.6)	-	-	6	(1.1)
Ear disorder	2	(0.4)	-	-	6	(1.1)
Nonotic						
Body as a whole						
Headache	45	(8.4)	26	(8.5)	43	(8.0)
Pain	12	(2.2)	6	(2.0)	9	(1.7)
Infection	8	(1.5)	7	(2.3)	13	(2.4)
Cold syndrome	5	(0.9)	5	(1.6)	5	(0.9)
Injury, accidental	5	(0.9)	5	(1.6)	1	(0.2)
Pain, abdomen	5	(0.9)	3	(1.0)	6	(1.1)
Surgical/medical procedure	4	(0.7)	3	(1.0)	1	(0.2)
Fever	3	(0.6)	3	(1.0)	6	(1.1)
Digestive system						
Diarrhea	10	(1.9)	-	-	4	(0.7)
Vomiting	7	(1.3)	4	(1.3)	5	(0.9)
Nausea	6	(1.1)	3	(1.0)	6	(1.1)
Dyspepsia	1	(0.2)	3	(1.0)	4	(0.7)
Respiratory system						
Rhinitis	22	(4.6)	8	(2.6)	17	(3.2)
Cough, increased	13	(2.4)	1	(0.3)	9	(1.7)
Pharyngitis	13	(2.4)	9	(3.0)	17	(3.2)
Skin and appendages						
Dermatitis	2	(0.4)	3	(1.0)	5	(0.9)

Adapted from Summary of Clinical Safety, Module 2, Volume 3, Table 2.7.4.7.3-7

The most frequently reported adverse events in patients receiving Ciprodex were headache (8.4%), rhinitis (4.6%), otitis media (3.7%), otitis externa in the nonstudy ear (3.5%), increased cough (2.4%), pharyngitis (2.4%), nonotic pain (2.2%), and ear pruritis (2.0%). Except for a single report of prostate cancer in an elderly Cortisporin patient, the reported adverse events in the AOE studies were considered by investigators to be nonserious and generally mild to moderate in intensity.

Comment: The adverse event profiles are similar across study groups. Most of the reported nonotic adverse events are unlikely to be related to a topical study therapy. Attribution of causality is more difficult for the otic adverse events. Otitis media and otitis externa in the nonstudy ear are not related to study therapy. Events such as ear pruritis and ear pain, however, could be related to study therapy but are also common manifestations of AOE.

The applicant analyzed adverse events by age, sex, and race. Adverse events were reported more commonly in adults (47.5% with adverse events) than in children (33.5%) or adolescents (33.9%). Both otic and nonotic adverse events were reported more frequently in adults. The most common otic adverse events in adults were ear pruritis, ear congestion, and otitis externa in the nonstudy ear. The most common otic adverse events in children and adolescents were otitis media and otitis externa in the nonstudy ear. The most common nonotic adverse event in each of these groups was headache. Adverse events were reported in 5 of 7 (71.4%) of infants and toddlers and were similar in nature to those reported in children. Only 9 of 34 (26.5%) elderly patients reported adverse events; these reports were similar in nature to those of adults.

Comment: Within each age group, there were no significant differences across treatments in the incidence or types of adverse events.

The incidence of adverse events was similar in males and females (37.8% and 39.8%, respectively). Adverse events were reported in 38.7% of white patients, 33.9% of black patients, and 42.6% of patients categorized as "other" (primarily Hispanic).

Comment: Within gender and race categories, there were no significant differences across treatments in the incidence or types of adverse events.

7.2.3.1.2.2. Acute Otitis Media in Patients with Tympanostomy Tubes

Table 51 shows adverse events occurring in >1% of treatment group in the pooled AOMT studies. Adverse events were reported in 186 of 400 Ciprodex patients (46.5%), 51 of 98 Ciloxan patients (52.0%), and 165 of 302 ofloxacin patients (54.6%).

Table 51: Adverse Events Occurring in ≥1% of Any Group: Pooled AOMT Studies

	Ciprodex (N=400)		Ciloxan (N=98)		Ofloxacin (N=302)	
	n	(%)	n	(%)	n	(%)
Otic						
Otitis media (nonstudy ear)	29	(7.3)	9	(9.2)	35	(11.6)
Pain, ear	22	(5.5)	8	(8.2)	18	(6.0)
Discomfort, ear	12	(3.0)	1	(1.0)	6	(2.0)
Discharge, ear	8	(2.0)	1	(1.0)	8	(2.6)
Device extrusion	7	(1.8)	-	-	9	(3.0)
Device blockage	6	(1.5)	-	-	7	(2.3)
Ear debris	3	(0.8)	-	-	6	(2.0)
Precipitate, ear	2	(0.5)	3	(3.1)	3	(1.0)
Pruritis, ear	2	(0.5)	1	(1.0)	3	(1.0)
Ear disorder	2	(0.5)	2	(2.0)	-	-
Nonotic						
Body as a whole						
Fever	34	(8.5)	7	(7.1)	28	(9.3)
Infection	18	(4.5)	7	(7.1)	13	(4.3)
Pain	10	(2.5)	3	(3.1)	4	(1.3)
Cold syndrome	7	(1.8)	-	-	7	(2.3)
Pain, abdomen	5	(1.3)	-	-	4	(1.3)
Headache	3	(0.8)	1	(1.0)	5	(1.7)
Flu syndrome	3	(0.8)	1	(1.0)	3	(1.0)
Injury, accidental	2	(0.5)	2	(2.0)	2	(0.7)
Asthenia	1	(0.3)	1	(1.0)	-	-
Digestive system						
Vomiting	9	(2.3)	-	-	9	(3.0)
Diarrhea	7	(1.8)	3	(3.1)	9	(3.0)
Nervous system						
Irritability	7	(1.8)	5	(5.1)	7	(2.3)
Crying	1	(0.3)	1	(1.0)	1	(0.3)
Respiratory system						
Rhinitis	25	(6.3)	7	(7.1)	15	(5.0)
Cough, increased	12	(3.0)	3	(3.1)	15	(5.0)
Pharyngitis	5	(1.3)	3	(3.1)	6	(2.0)
Sinusitis	4	(1.0)	1	(1.0)	1	(0.3)
Asthma	1	(0.3)	3	(3.1)	3	(1.0)
Bronchitis	1	(0.3)	2	(2.0)	2	(0.7)
Pneumonia	-	-	1	(1.0)	3	(1.0)
Lung disorder	-	-	1	(1.0)	-	-
Skin and appendages						
Dermatitis	3	(0.8)	1	(1.0)	4	(1.3)
Erythema	1	(0.3)	1	(1.0)	1	(0.3)
Pruritis	1	(0.3)	2	(2.0)	-	-
Special senses						
Taste perversion	4	(1.0)	-	-	3	(1.0)
Conjunctivitis	4	(1.0)			2	(0.7)
Lid margin, crusting	-	-	1	(1.0)	-	-

Adapted from Summary of Clinical Safety, Module 2, Volume 3, Table 2.7.4.7.3-4

The most frequently reported adverse events in patients receiving Ciprodex were fever (8.5%), otitis media in the nonstudy ear (7.3%), rhinitis (6.3%), ear pain (5.5%), infection (primarily upper respiratory, 4.5%), ear discomfort (3.0%), increased cough (3.0%), nonotic pain (2.5%), vomiting (2.3%), and ear discharge (2.0%). The reported adverse events were generally considered by investigators to be nonserious and mild to moderate in intensity.

> *Comment: Adverse events were reported more frequently in the AOMT studies than in the AOE studies. Many of the more commonly reported adverse events in the AOMT population, such as fever, contralateral otitis media, rhinitis, and ear pain, are concurrent manifestations of associated upper respiratory infections and the underlying disease process. The adverse event profiles are generally similar across study groups.*

The applicant analyzed adverse events by age, sex, and race. Adverse events were reported more commonly in infants and toddlers (59.2%) than in children (42.0%). The number of otic adverse events was similar between groups, but nonotic events were reported more commonly in infants and toddlers. The most common otic adverse event in infants and toddlers was otitis media in the nonstudy ear, and the most common nonotic events were fever and rhinitis. The most common otic adverse events in children were ear pain and otitis media in the nonstudy ear, and the most common nonotic events were pain and fever.

> *Comment: Infants and toddlers are more likely to have nonspecific systemic symptoms in association with AOMT than are older children. Within each age group, there were no significant differences across treatments in the incidence or types of adverse events.*

The incidence of adverse events was similar in males and females (49.7% and 51.1%, respectively). Adverse events were reported in 50.8% of white patients, 42.9% of black patients, and 50.0% of patients categorized as "other" (primarily Hispanic).

> *Comment: Within gender and race categories, there were no significant differences across treatments in the incidence or types of adverse events.*

7.2.3.2. Treatment-Related Adverse Events

7.2.3.2.1. Phase 1 Studies

No adverse events in the phase 1 studies were determined by the investigators to be possibly, probably, or definitely related to the test articles.

7.2.3.2.2. Phase 2 and 3 Studies

Comment: For the phase 2 and 3 studies, treatment-related adverse event summaries are presented by indication.

7.2.3.2.2.1. Acute Otitis Externa

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 52.

Table 52. Treatment-Related Adverse Events: Pooled AOE Studies

	Ciprodex (N=537)		Ciloxan (N=305)		Cortisporin (N=535)	
	n	(%)	*n*	(%)	*n*	(%)
Otic						
Pruritis, ear	8	(1.5)	4	(1.3)	15	(2.8)
Ear debris	3	(0.6)			2	(0.4)
Infection, superimposed ear	3	(0.6)				
Ear congestion	2	(0.4)	1	(0.3)	4	(0.7)
Pain, ear	2	(0.4)			1	(0.2)
Discomfort, ear	1	(0.2)			6	(1.1)
Hearing, decreased	1	(0.2)			3	(0.6)
Ear disorder	1	(0.2)			2	(0.4)
Erythema, canal					1	(0.2)
Nonotic						
Body as a whole						
Headache			1	(0.3)		
Digestive system						
Nausea					1	(0.2)
Skin and appendages						
Erythema	2	(0.4)				
Dermatitis			1	(0.3)	1	(0.2)

Adapted from Summary of Clinical Safety, Module 2, Volume 2, Tables 2.7.4.2.1-2 and 2.7.4.2.1-6

The most frequently reported treatment-related adverse event in Ciprodex patients was ear pruritis (1.5%). All of the reported treatment-related adverse events were considered to be nonserious and mild to moderate in intensity with the exception of severe ear discomfort (burning) in one Cortisporin patient.

*Comment: The **ADVERSE REACTIONS** section of the proposed labeling for the AOE indication contains all of the reported Ciprodex-related adverse events. A table shows the treatment-related adverse events which occurred in ≥0.4% of Ciprodex patients, followed by text listing the events which occurred in a single patient. This display is acceptable.*

7.2.3.2.2.2. Acute Otitis Media in Patients with Tympanostomy Tubes

Adverse events determined by the investigators to be possibly, probably, or definitely related to trial treatment are listed in Table 53.

Table 53: Treatment-Related Adverse Events: Pooled AOMT Studies

	Ciprodex (N=400)		Ciloxan (N=98)		Ofloxacin (N=302)	
	n	(%)	n	(%)	n	(%)
Otic						
Discomfort, ear	12	(3.0)	1	(1.0)	3	(1.0)
Pain, ear	9	(2.3)	1	(1.0)	9	(3.0)
Precipitate, ear	2	(0.5)	3	(3.1)	3	(1.0)
Pruritis, ear	1	(0.3)	1	(1.0)	2	(0.7)
Device blockage	1	(0.3)				
Tinnitus	1	(0.3)				
Infection, superimposed ear					2	(0.7)
Irritation, ear					2	(0.7)
Ear debris					1	(0.3)
Edema, eardrum					1	(0.3)
Hyperemia, eardrum					1	(0.3)
Nonotic						
Body as a whole						
Headache					1	(0.3)
Digestive system						
Monilia, oral	1	(0.3)			1	(0.3)
Diarrhea					1	(0.3)
Nervous system						
Irritability	2	(0.5)				
Crying	1	(0.3)	1	(1.0)	1	(0.3)
Dizziness	1	(0.3)				
Respiratory system						
Cough, increased					1	(0.3)
Skin and appendages						
Erythema	1	(0.3)				
Special senses						
Taste perversion	2	(0.5)			3	(1.0)

Adapted from C-99-59 study report, Volume 3,Table 14.3.1.6-1 and C-00-52 study report, Volume 7, Table 14.3.1.6-1

The most frequently reported treatment-related adverse events in Ciprodex patients were ear discomfort (burning, stinging; 3.0%) and ear pain (2.3%). All of the treatment-related adverse events were considered to be nonserious and mild to moderate in intensity.

*Comment: The **ADVERSE REACTIONS** section of the proposed labeling for the AOMT indication contains all of the reported Ciprodex-related adverse events. A table shows the treatment-related adverse events which occurred in ≥0.5% of Ciprodex patients, followed by text listing the events which occurred in a single patient. This display is acceptable.*

7.2.3.3. Discontinuations Due to Adverse Events

7.2.3.3.1. Phase 1 Studies

In the skin sensitization study, 17 of the 574 subjects (3.0%) were discontinued because of adverse events: 6 of 231 (2.6%) who received Ciprodex, 6 of 114 (5.3%) who received Ciloxan, 2 of 114 (1.8%) who received Maxidex, and 3 of 115 (2.6%) who received saline. The investigators determined that these events were unrelated to the test articles.

All 11 Ciprodex recipients completed the single-dose pharmacokinetic study.

7.2.3.3.2. Phase 2 and 3 Studies

In the AOE studies, 54 of the 1377 patients (3.9%) were discontinued because of adverse events: 20 of 537 (3.7%) who received Ciprodex, 13 of 303 (4.3%) who received Ciloxan, and 21 of 535 (3.9%) who received Cortisporin. The most frequently reported adverse event that resulted in discontinuation from the study was otitis media. Two Ciprodex patients were discontinued because of treatment-related adverse events; both developed fungal superinfections.

In the AOMT studies, 97 of the 800 patients (12.1%) were discontinued because of adverse events: 39 of 400 (9.8%) who received Ciprodex, 12 of 98 (12.2%) who received Ciloxan, and 46 of 302 (15.2%) who received ofloxacin. The most frequently reported adverse event that resulted in discontinuation from the study was otitis media in the nonstudy ear. Three patients were discontinued because of treatment-related adverse events: one Ciprodex patient with ear discomfort (burning), one Ciloxan patient with crying, and one ofloxacin patient with ear irritation.

7.2.3.4. Serious Adverse Events

7.2.3.4.1. Phase 1 Studies

In the skin sensitization study, 14 serious adverse events were reported in 6 subjects: renal carcinoma in a Ciprodex subject; urinary tract infection in a Ciloxan subject; flu syndrome and dyspnea in a Ciloxan subject; aseptic meningitis with headache, neck pain, back pain, myalgia, and nausea in a Maxidex subject; squamous cell carcinoma of the leg and surgical/medical procedure (biopsy) in a saline subject; and an allergic reaction with skin discoloration and dermatitis that were attributed to use of ceftriaxone to treat a urinary tract infection in a saline subject. The investigators determined that these events were unrelated to the test articles.

None of the Ciprodex recipients in the pharmacokinetic studies had a serious adverse event.

7.2.3.4.2. Phase 2 and 3 Studies

No serious adverse events were reported in the Ciprodex patients in the AOE studies. A 79 year old Cortisporin patient was diagnosed with prostate cancer following study drug treatment. This event was determined to be unrelated to the study drug.

Four serious adverse events were reported in the AOMT studies. An 11 month old Ciprodex patient was hospitalized for 4 days for severe abdominal pain that began following the completion of study therapy but before the test of cure visit. The pain resolved with antacid treatment, and the patient completed the study. A 1 year old Ciloxan patient was hospitalized with pneumonia on study day 8 and responded well to therapy. A 1 year old ofloxacin patient was hospitalized with severe pneumonia following the completion of study therapy but before the test of cure visit. The pneumonia resolved with antimicrobial therapy, and the patient completed the study. Another 1 year old ofloxacin patient was hospitalized for 5 days for cellulitis of the left foot following an insect bite. This patient was discontinued from the study. These serious adverse events were determined by the investigators and medical monitor to be unrelated to study drug treatment.

7.2.3.5. Deaths

No deaths were reported in any of the studies reviewed.

7.2.4. Additional Safety Studies

7.2.4.1. Skin Sensitization Study

Protocol C-97-56 was performed to evaluate the potential of Ciprodex, ciprofloxacin (Ciloxan) alone, or dexamethasone (Maxidex) alone to induce delayed contact hypersensitivity in healthy subjects. Participants in this study were to receive nine applications of a topical patch over a 21-day induction period, followed by a 2-week rest period, and then a 48-hour challenge application at another site. Total enrollment was 574 subjects, 231 who received Ciprodex, 114 who received Ciloxan, 114 who received Maxidex, and 115 who received a saline control. The per protocol population comprised the 468 subjects (Ciprodex, 191; Ciloxan 89; Maxidex, 95; and saline, 93) who met inclusion criteria and had adequate induction and challenge periods. There was no evidence of development of delayed contact sensitization in any of these subjects. Low levels of contact irritation were noted with each test article during the induction period; mean inflammation scores during induction ranged from 0.03 to 0.14 on a scale of 0 to 3 (none = 0, mild = 1, moderate = 2, severe = 3).

7.2.4.2. Audiometry

In the AOMT studies, audiometric examinations, including determination of speech reception threshold and bone and air conduction audiometry, were performed at study entry and exit in patients 4 to 12 years of age. Speech reception thresholds were determined in 124 patients, 69 who received Ciprodex, 15 who received Ciloxan, and 40 who received ofloxacin. Speech reception thresholds improved in all treatment groups.

In each trial, the difference between groups was not significant. Bone and air conduction audiometry was performed in 132 patients, 71 who received Ciprodex, 16 who received Ciloxan, and 45 who received ofloxacin. One Ciprodex patient in Protocol C-00-52 had a decrease in hearing from baseline at the test of cure visit but had no clinically relevant hearing decrease at follow-up 7 weeks later. At the test of cure visit, this child was noted to be ill and uncooperative with testing, and the audiometry results were reported to be inconsistent. No patient in any group had a clinically relevant hearing decrease from baseline.

7.2.5. Safety Update

In the four-month safety update, submitted 1/22/03, the applicant stated that there were no new or ongoing clinical trials of Ciprodex and no new clinical safety data. The applicant also submitted a technical report of an animal study to support the statement in the proposed label, "No signs of local irritation were found when CIPRODEX® Otic was applied topically in the rabbit eye."

7.2.6. Conclusions

In the AOE studies, the most frequently reported adverse events in patients receiving Ciprodex were headache (8.4%), rhinitis (4.6%), otitis media (3.7%), otitis externa in the nonstudy ear (3.5%), increased cough (2.4%), pharyngitis (2.4%), nonotic pain (2.2%), and ear pruritis (2.0%). These events were generally considered to be mild to moderate in intensity. Most of these adverse events are symptoms or manifestations of the underlying disease process or a concurrent illness and are not related to study drug administration. The most frequently reported treatment-related adverse event in Ciprodex patients was ear pruritis (1.5%). Other treatment-related adverse events included ear debris (0.6%), superimposed ear infection (0.6%), ear congestion (0.4%), ear pain (0.4%), erythema (0.4%), and single reports of ear discomfort, decreased hearing, and ear disorder (tingling). All of the treatment-related adverse events were considered to be mild to moderate in intensity. Two Ciprodex patients were discontinued because of treatment-related adverse events; both developed fungal superinfections. No serious adverse events were reported in Ciprodex patients in these studies.

In the AOMT studies, the most frequently reported adverse events in patients receiving Ciprodex were fever (8.5%), otitis media in the nonstudy ear (7.3%), rhinitis (6.3%), ear pain (5.5%), infection (primarily upper respiratory, 4.5%), ear discomfort (3.0%), increased cough (3.0%), nonotic pain (2.5%), vomiting (2.3%), and ear discharge (2.0%). These events were generally considered by investigators to be nonserious and mild to moderate in intensity. Most of these adverse events are symptoms or manifestations of the underlying disease process or a concurrent illness and are not related to study drug administration. The most frequently reported treatment-related adverse events in Ciprodex patients were ear discomfort (burning, stinging; 3.0%) and ear pain (2.3%). Other treatment-related adverse events included ear precipitate (residue, 0.5%), irritability (0.5%), taste perversion (0.5%), and single reports of tympanostomy tube blockage, ear pruritis, oral moniliasis, crying, dizziness, and erythema. All of the

treatment-related adverse events were considered to be mild to moderate in intensity. One Ciprodex patient was discontinued because of treatment-related ear discomfort (burning). One Ciprodex patient had a serious adverse event (abdominal pain) that was determined to be unrelated to study therapy. No serious treatment-related adverse events were reported in Ciprodex patients in these studies.

The reported Ciprodex-related adverse events are similar in incidence and type to those reported with the approved comparator drugs in these studies. They are also similar in incidence and type to the adverse events listed in the package inserts of these and other recently approved topical antimicrobials. Ciprofloxacin and hydrocortisone otic suspension (CIPRO® HC OTIC) is approved for the treatment of AOE. The treatment-related adverse events listed in the **ADVERSE REACTIONS** section of the labeling include headache (1.2%), pruritis (0.4%), and single reports of migraine, hypesthesia, paresthesia, fungal dermatitis, cough, rash, urticaria, and alopecia. Ofloxacin otic solution (FLOXIN® Otic) is approved for the treatment of AOE, AOMT, and chronic suppurative otitis media (CSOM) with perforated tympanic membranes. There are two **ADVERSE REACTIONS** listings, one for AOE, in which the tympanic membrane is intact, and one for AOMT and CSOM, in which the tympanic membrane is not intact. For AOE, the treatment-related adverse events listed include pruritis (4%), application site reaction (3%), dizziness (1%), earache (1%), vertigo (1%), and single reports of dermatitis, eczema, erythematous rash, hypoaesthesia, tinnitus, dyspepsia, hot flushes, flushing, and otorrhagia. For AOMT and CSOM, the treatment-related adverse events listed include taste perversion (7%), earache (1%), pruritis (1%), paraesthesia (1%), rash (1%), dizziness (1%), diarrhea (0.6%), nausea (0.3%), vomiting (0.3%), dry mouth (0.5%), headache (0.3%), vertigo (0.5%), otorrhagia (0.5%), tinnitus (0.3%), fever (0.3%), and single reports of application site reaction, otitis externa, urticaria, abdominal pain, dysaesthesia, hyperkinesia, halitosis, inflammation, pain, insomnia, coughing, pharyngitis, rhinitis, sinusitis, and tachycardia.

Ciprodex is safe and well-tolerated in the treatment of AOE and AOMT. The proposed labeling lists adverse reactions by indication and includes all of the treatment-related adverse events reported in study patients who received Ciprodex.

8. Dosing, Regimen, and Administration Issues

The proposed dosage for all patients with AOE or AOMT is 4 drops (0.14 mL; 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for 7 days. In both AOE studies and the AOMT study C-99-59, pediatric patients received a dose of 3 drops, and in C-00-52, they received a dose of 4 drops. The applicant indicated that the decision to change the dosage in pediatric patients to 4 drops was in response to feedback from participants in the earlier studies. Three-drop doses were effective in pediatric patients. The four-drop dose was effective and safe in C-00-52. There is no additional toxicity with the four-drop dose; it is acceptable for all patients with AOE or AOMT.

A patient information sheet contains instructions for administration of the suspension. Patients or caregivers are advised to warm the bottle of suspension in the hand for 1 or 2 minutes before administering the drops. For patients with AOMT, it is important to pump the tragus to ensure delivery of the suspension through the tympanostomy tube. Patients are advised to lie on their side for at least 60 seconds following instillation of the drops.

9. Use in Special Populations

9.1. Age, Gender, and Race Effects

The applicant provided efficacy and safety analyses by age, gender, and race.

In the AOE studies, cure rates were approximately 6% to 12% greater for pediatric patients compared with adults. Few elderly patients were enrolled; cure rates were similar to those for other adults. Adverse events were reported more commonly in adults than in children. Elderly patients had fewer adverse events than other adults. There were no significant differences in efficacy or safety within age groups across drug treatments.

The AOMT studies were performed only in pediatric patients. Cure rates were approximately 7% to 10% lower for infants and toddlers than for older children. Adverse events were reported more commonly in infants and toddlers than in older children. Across drug treatments, subgroup analyses by age were similar to the overall efficacy and safety analyses.

For each indication, there were no significant differences in the efficacy or safety of each study drug when data were analyzed by gender or race (white, black, other). Across drug treatments, subgroup analyses by gender or race were similar to the overall efficacy and safety analyses.

9.2. Pediatric Program

AOE is common in children, and AOMT occurs almost exclusively in children. All relevant pediatric age groups have been studied in this NDA; no additional pediatric data are needed.

10. Conclusions and Recommendations

Acute Otitis Externa

The applicant has submitted two studies demonstrating that Ciprodex (ciprofloxacin 0.3% and dexamethasone 0.1%) otic suspension is noninferior to the approved comparator Cortisporin (neomycin 0.35%, polymyxin B 10,000 IU/mL, hydrocortisone 1.0%) otic suspension for the treatment of acute otitis externa (AOE) in pediatric and adult patients. The applicant did not demonstrate the superiority of the combination over ciprofloxacin alone, however. In the AOE studies, the most frequently reported Ciprodex-related

adverse event was ear pruritis (1.5%). No serious adverse events were reported in Ciprodex patients in these studies.

Ciprodex is at least as effective as the Cortisporin antibiotic-steroid combination for AOE, and it was demonstrated to be effective in acute otitis media in patients with tympanostomy tubes (AOMT). Ciprodex may be approved for the treatment of AOE due to *Pseudomonas aeruginosa* and *Staphylococcus aureus* in pediatric (age 6 months and older), adult, and elderly patients.

Acute Otitis Media in Patients with Tympanostomy Tubes

The applicant has submitted two studies demonstrating that Ciprodex is effective for the treatment of AOMT. The first study showed that the combination product was superior to ciprofloxacin alone for a clinically significant endpoint, time to cessation of otorrhea. The second study showed noninferiority to the approved comparator ofloxacin 0.3% otic solution. In the AOMT studies, the most frequently reported Ciprodex-related adverse events were ear discomfort (stinging, burning; 3.0%) and ear pain (2.3%). No serious treatment-related adverse events were reported in Ciprodex patients.

These studies support approval of Ciprodex for the treatment of AOMT due to *S. aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *P. aeruginosa* in pediatric patients 6 months to 12 years of age.

Thomas Smith, M.D.
Medical Officer, HFD-520

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NDA review; indications AOE, AOMT
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