CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-537

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology & Biopharmaceutics Review

NDA	21-537
PRODUCT	Ciprofloxacin 0.3% and Dexamethasone 0.1%
TRADE NAME	CIPRODEX®
FORMULATION	Otic suspension
SUBMISSION DATE	September 23, 20002
SUBMISSION TYPE	Original application
SPONSOR	Alcon Research, Ltd. 6501 South Freeway Fort Worth, Texas 76134-2099
REVIEWER	Paul W. Buehler, Pharm.D., Ph.D.
ACTING TEAM LEADER	Philip M. Colangelo, Pharm.D., Ph.D.

I. Executive Summary

The sponsor is submitting NDA 21-537 to seek approval of CIPRODEX® Otic (ciprofloxacin 0.3% and dexamethasone 0.1% otic suspension) for the treatment of (1) Otis Externa and (2) treatment of Acute Otis Media Tympanostomy (AOMT) tubes. Both indications are for patients age 6 months and older. Currently, several topical products are available for the treatment of Otis Externa including CIPRO® HC Otic, CORTISPORIN®-TC Otic and FLOXIN® Otic. However, only FLOXIN® Otic solution is currently indicated for the treatment of AOMT caused by *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Pseudomonas aeruginosa.*

Orally administered, fluoroquinolones are generally not used in pediatrics due to the potential for cartilage erosion in weight bearing joints shown to occur in certain young animal species. An exception to this general practice is treating infections caused by *Pseudomonas aeruginosa* in pediatric and adolescent patients suffering from cystic fibrosis. Pharmacokinetic studies in pediatric patients receiving oral doses of fluoroquinolones demonstrate comparable exposures to adults.

Serum ofloxacin concentrations following single dose studies using 0.3% FLOXIN® otic solution in patients with tympanostomy tubes, with and without otorrhea, were 4.1 ng/mL and 5.4 ng/mL, respectively. Serum concentrations of ofloxacin were approximately 300 fold less with otic administration of 0.3% FLOXIN® solution (5 drops bilaterally 1.5 mg) than that observed with a single oral dose of 200 mg (1.5 µg / mL).

The primary concern with systemic absorption of dexamethasone from the CIPRODEX® Otic dosage form is suppression of the hypothalamo-pituitary-adrenal axis. Typical oral dexamethasone doses in adults range from 0.5 – 9 mg/day depending on the condition being treated. The dose being evaluated for exposure from a single administration is 280 µg of dexamethasone (4 drops CIPRODEX® administered bilaterally).

The systemic absorption of both ciprofloxacin and dexamethasone from CIPRODEX® Otic after a single four-drop application in pediatric and young adult patients following typanostomy tube placement was determined in study C-00-68 performed at two sites. Site I was located at [redacted] while site II was located at [redacted] A majority of the patients were enrolled at site I, however, several patients were enrolled at site II. The same study also evaluated the effect of dexamethasone on the absorption of ciprofloxacin by employing a study arm to evaluate the systemic absorption of ciprofloxacin

following a four drop application of CILOXAN®, an ophthalmic preparation containing 0.3% ciprofloxacin in solution without dexamethasone.

Pharmacokinetic data for study C-00-68 providing pivotal information regarding systemic exposure to both ciprofloxacin and dexamethasone following administration of CIPRODEX® Otic to patients with tympanostomy tubes collected at study site I was deemed unacceptable by the Division of Scientific Investigation (DSI). DSI's audit of protocol C-00-68 as carried out at site I concluded that data falsification, protocol violations and incomplete/unverifiable study patient records caused pharmacokinetic data to be suspect and therefore not usable in support of NDA 21-537. Findings and conclusions were communicated by DSI on March 21, 2003 in a memo appended to the NDA submission and appendix C of this review.

The evaluation of systemic exposure to ciprofloxacin and dexamethasone in pediatric and young adult patients with typanostomy tubes treated with a one-time dose consisting of eight drops of CIPRODEX® Otic (4 drops bilaterally) is solely addressed by study C-02-58. The study includes five patients evaluated at study site II under protocol C-00-68 and six additional patients also evaluated at site II. The 6 additional patients were enrolled following an agreement between the Division of Anti-infective Drug Products and the Sponsor. The study addresses the absorption and systemic exposure of 840 µg of ciprofloxacin and 280 µg of dexamethasone from CIPRODEX® Otic in the newly enrolled patients and 5 patients previously evaluated at site II.

Efficacy studies conducted by Alcon in support of NDA 21-537 compared the following combinations of drugs to treat patients with (1) AOTM with otorrhea of 3 weeks or less duration or (2) mild, moderate and severe AOE.

Study #	Drug	Dosing/Schedule	Duration
[redacted]	CIPRODEX® Otic suspension	3 drops BID	7 days
	CILOXAN® solution	3 drops BID	7 days
[redacted]	CIPRODEX® Otic suspension	4 drops BID	7 days
	FLOXIN® Otic solution	5 drops BID	10 days
[redacted]	CIPRODEX® Otic suspension	3 drops BID†	7 days
	CILOXAN® solution	3 drops BID†	7 days
	CORTISPORIN® Otic suspension	3 drops TID†	7 days
[redacted]	CIPRODEX® Otic suspension	3 drops BID†	7 days
	CORTISPORIN® Otic suspension	3 drops TID†	10 days

† Indicates the pediatric dose utilized. Adults were dosed with 4 drops of one of the 3 solutions BID indicated in study C-98-18.

The systemic absorption of ciprofloxacin (0.840 mg) and dexamethasone (0.280 mg) following ototopical administration of 8 drops (4 drops bilaterally) of Ciprodex® suspension to patients (1-12 years of age) immediately following typanostomy tube placement was evaluated.

The mean maximal (±SD) ciprofloxacin concentrations (1.39 ± 0.88 ng/mL) were generally lower than maximal ofloxacin concentrations observed in two separate studies [redacted] ng/mL) following ototopical administration of Floxin® otic solution when both preparations were administered though typanostomy tubes. Floxin® otic solution has been marketed since 1998 for the treatment of acute otitis media in patients ages 1 year and older. Therefore, any risk to patients (1 year and older), based on exposure to ciprofloxacin in the Ciprodex® dosage form should not exceed the risk following ototopical administration of Floxin® otic solution.

The mean maximal (±SD) dexamethasone concentration (1.14 ± 1.54 ng/mL) was approximately 7 times less than that reported in the literature following oral administration of a single dose 0.5 mg tablet to normal adult females. The range of maximal dexamethasone concentrations following ototopical administration of Ciprodex® suspension was — ng/mL. The Sponsor speculates that the patient exhibiting a maximal dexamethasone concentration of — .g/mL was actually treated with a low dose of IV dexamethasone at some point during the study. However, the patient demonstrated no quantifiable dexamethasone in the baseline sample and no record of IV dexamethasone administration was provided. The possibility therefore exists that the patient truly did absorb a greater than expected amount of dexamethasone via ototopical administration of Ciprodex® suspension. A plasma concentration of — ng/mL represents a value nearing the maximal dexamethasone concentration following an oral 0.5 mg tablet administration (7.9 ± 1.0 ng/mL).

The peak plasma concentrations of ciprofloxacin and dexamethasone observed following the ototopical dose of Ciprodex (0.840 mg ciprofloxacin and 0.240 mg dexamethasone) to patients with otitis media with typanostomy tubes were approximately 0.1% and 14% seen following a 250 mg ciprofloaxcin and a 0.5 mg dexamethasone oral tablet dose, respectively. The concentrations of ciprofloxacin and dexamethasone do not appear to warrant concern of toxicity issues such as arthropathy or HPA axis supression arising from initial peak plasma concentrations or accumulation of ciprofloxacin or dexamethasone following seven days of ototopical dosing.

A. Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation III (OCPB/DPE III) has reviewed NDA 21-537. The submission is acceptable from a Clinical Pharmacology point of view.

Paul W. Buehler, Pharm.D., Ph.D.
Office of Clinical Pharmacology/Biopharmaceutics, Division of Pharmaceutical Evaluation III

RD/FT Initialed by Philip M. Colangelo, Pharm.D., Ph.D., _____
Acting Team Leader

cc:
Division File: NDA 50-582
HFD-520 (CSO/Nguyen)
HFD-520 (MO/Smith)
HFD-880 (Division File, Lazor, Selen, Colangelo, Buehler)
CDR (Clin. Pharm./Biopharm.)

B. Phase IV Commitments:

There are no Phase IV commitments

Table of Contents

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

Absorption of ciprofloxacin and dexamethasone from a single bilateral ototopically administered dose of Ciprodex® (4 drops each ear) providing 0.840 mg of ciprofloxacin and 0.280 mg of dexamethasone was evaluated in 11 pediatric patients (ages 1-12 years) undergoing typanostomy surgery.

Patients were dosed immediately following typanostomy tube placement and blood was sampled 5 and 30 minutes prior to ototopical administration then at 0.25, 0.5, 1.0, 2.0, 4.0 and 6.0 hours following dosing. Plasma samples were analyzed separately for ciprofloxacin and dexamethasone by a validated LC/MS/MS method with a limit of quantitation (LOQ) for each drug substance equal to ng/mL, respectively. Systemic exposure to ciprofloxacin and dexamethasone was determined by pharmacokinetic model independent methods.

Nine of the eleven total patients enrolled in PK studies were used in the determination of ciprofloxacin absorption. Mean (± SD) maximal ciprofloxacin plasma concentrations (1.39 ± 0.88 ng/mL) occurred between 15 minutes and 134 minutes following Ciprodex® administration and ranged from .. Ciprofloxacin persisted in the plasma of two patients at the 6-hour post administration time point with values near the limit . For two patients, samples were not available, while the remaining five patients demonstrated concentrations of ciprofloxacin below the LOQ. Mean (± SD) AUC_{0-4} and AUC_{0-6} values were 4.96 ± 2.30 ng • hr/mL (n=6) and 8.53 ng • hr/mL (n=2), respectively.

Nine of the eleven total patients enrolled in PK studies were used in the determination of dexamethasone absorption. One patient did not demonstrate any absorption of dexamethasone at any time point following administration. One patient (#205 / 00-68) was dosed with IV dexamethasone during surgery thus removed from analysis. Additionally, a third patient (#206 / 02-58) appears to have been administered a small dose of IV dexamethasone at some point during surgery. However, there is no quantifiable concentration in the patient's baseline plasma sample according to the investigators reported results and no record of the patient receiving an IV dose of dexamethasone. Thus there is no basis for excluding this patient from analysis unless the investigator can provide a reasonable explanation for this observation.

Mean (± SD) maximal dexamethasone plasma concentrations (1.14 ± 1.54 ng/mL) occurred between 10 minutes and 125 minutes following Ciprodex® administration and ranged from ng/mL. Dexamethasone persisted in the plasma of five patients at the 6-hour post administration time point. The mean (± SD) dexamethasone concentration at the 6-hour post administration time point was 0.332 ± 0.228 ng/mL and values ranged from For two patients at 6 hours post administration, samples were not available, while the remaining 2 patients demonstrated concentrations of dexamethasone below the LOQ. Mean (± SD) AUC_{0-4} and AUC_{0-6} values were 2.64 ± 2.53 ng • hr/mL (n=8) and 4.94 ± 2.95 ng • hr/mL, respectively.

The commonly recommended oral dose of Ciprofloxacin for the treatment of several Gram positive and Gram negative infections in adult patients is 500-mg every 12 hours. The mean serum C_{max} and AUC values following a 500-mg oral dose of ciprofloxacin are 2.4 µg/mL and 11.6 µg • hr/mL, respectively. Following ototopical administration of 8 drops of Ciprodex® the patients are exposed to 600 times less than a typical (500-mg) oral dose of ciprofloxacin. The mean (± SD) C_{max} (1.39 ± 0.88 ng/mL) following ototopical administration is approximately 1727 times less than that achieved with a typical (500 mg) oral dose of ciprofloxacin.

Oral Dexamethasone dosing varies widely depending on the condition being treated with initial doses ranging between 0.75 to 9 mg/day. Dexamethasone is approximately 30 times more potent than hydrocortisone as an anti-inflammatory corticosteroid, therefore drop for drop Ciprodex® (0.1%

dexamethasone) should provide approximately 3 times the anti-inflammatory potency of Cipro® HC (1% hydrocortisone). Cipro® HC does not have an indication for acute otitis media with otorrhea in patients with typanostomy tubes thus reducing the potential for systemic absorption of hydrocortisone and potential HPA axis suppression. Therefore, evaluation of systemic exposure to dexamethasone following ototopical administration of Ciprodex® in patients with typanostomy tubes was essential.

Few studies have evaluated the pharmacokinetics following low dose oral dexamethasone administration. Loew et al [Eur J Clin Pharmacol (1986) 30:225-230] evaluated the pharmacokinetics of dexamethasone following a 0.5 mg oral dose in normal health adult females. The mean (± SD) maximal plasma concentration was determined to be 7.9 ± 1.0 ng/mL. Following ototopical administration of 8 drops of Ciprodex®, patients are exposed to approximately one-half of the lowest oral dose of dexamethasone reported in the literature. The mean (± SD) dexamethasone C_{max} was determined to be 1.14 ± 1.54 ng/mL with a range of C_{max} values from [redacted] ng/mL. Therefore, based on limited comparative oral pharmacokinetic data the mean C_{max} for dexamethasone following ototopical administration of 0.28 mg resulted in a 7 fold lower concentration than that reported by Loew et al following a single oral dose of 0.5 mg. However, the lowest C_{max} observed in the 9 patients demonstrating quantifiable plasma concentrations of dexamethasone was 59 fold lower and highest C_{max} observed was 1.5 fold lower than that reported by Loew et al following a 0.5 mg oral dose. The highest C_{max} was seen in patient #206/02-58 and there is question regarding the previous exposure of this patient to IV dexamethasone. Without sufficient evidence from the investigator and Sponsor that the patient did truly receive an IV dose the data must be included in the revised labeling.

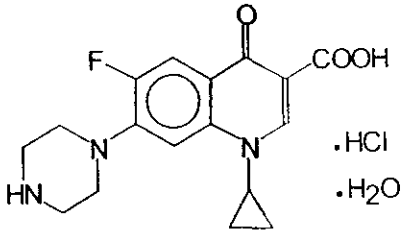
The peak plasma concentrations of ciprofloxacin and dexamethasone observed following the ototopical dose of Ciprodex (0.840 mg ciprofloxacin and 0.240 mg dexamethasone) to patients with otitis media with typanostomy tubes were approximately 0.1% and 14% seen following a 250 mg ciprofloaxcin and a 0.5 mg dexamethasone oral tablet dose, respectively. The concentrations of ciprofloxacin and dexamethasone do not appear to warrant concern of toxicity issues such as arthropathy or HPA axis supression arising from initial peak plasma concentrations or accumulation of ciprofloxacin or dexamethasone following seven days of ototopical dosing.

IV. Question Based Review

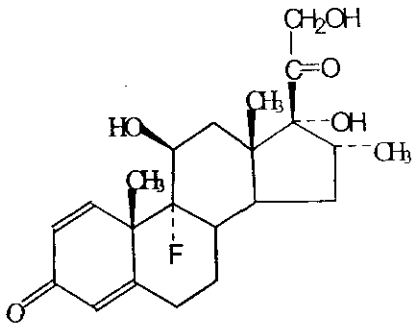
A. General Attributes

1. *What are the highlights of the chemistry and physical-chemical properties of ciprofloxacin and dexamethasone?*

Ciprofloxacin, a fluoroquinolone is available as the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The empirical formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and the structural formula is:



Dexamethasone, 9-fluoro-11(beta), 17, 21-trihydroxy-16(alpha)-methylpregna-1, 4-diene-3,20-dione, is an anti-inflammatory corticosteroid. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



What are the properties of the formulation of the drug product?

Clinical Formulation For Ciprodex® Suspension

Ciprofloxacin HCl	0.3%
Dexamethasone	0.1%
Benzalkonium Chloride	0.01%
Hydroxyethyl Cellulose	
Sodium Acetate	
Acetic Acid	
Sodium Chloride	
EDTA (Disodium)	
Tyloxapol	
Boric Acid	
Sodium Hydroxide	pH adjust
Hydrochloric Acid	pH adjust
Purified Water	

What are the proposed mechanisms of drug action and therapeutic indications?

Mechanism of drug action

Ciprofloxacin has *in vitro* activity against a wide range of gram-positive and gram-negative microorganisms. Dexamethasone has been added to aid in the resolution of the inflammatory response accompanying bacterial infection.

Therapeutic indications

Acute Otitis Media tympanostomy tubes in patients (age 6 months and older) due to

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

Dosage and Route of administration

The dose for both indications is four drops (0.14 mL, 0.42 mg ciprofloxacin, 0.14 mg dexamethasone) instilled into the affected ear twice daily for seven days.

B. General Clinical Pharmacology

1. *What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?*

The response end points were measured as resolution of clinical infection in patients with acute otitis media with otorrhea following administration of Ciprodex® through typanostomy tubes (studies C-99-59 and C-00-52) and resolution of clinical infection in patients with acute otitis externa following Ciprodex® administration to the external ear canal.

Study #	Drug	Dosing/Schedule	Duration
C-99-59 (AOMT)	CIPRODEX® Otic suspension	3 drops BID	7 days
	CILOXAN® solution	3 drops BID	7 days
C-00-52 (AOMT)	CIPRODEX® Otic suspension	4 drops BID	7 days
	FLOXIN® Otic solution	5 drops BID	10 days
C-98-18 (AOE)	CIPRODEX® Otic suspension	3 drops BID†	7 days
	CILOXAN® solution	3 drops BID†	7 days
	CORTISPORIN® Otic suspension	3 drops TID†	7 days
C-98-19 (AOE)	CIPRODEX® Otic suspension	3 drops BID†	7 days
	CORTISPORIN® Otic suspension	3 drops TID†	10 days

An undesired effect of ototopical administration of Ciprodex® is systemic absorption of ciprofloxacin and/or dexamethasone from the dosage form. The desired effect is to exert pharmacological activity at the site of application thereby minimizing systemic absorption.

2. *Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?*

The detection of ciprofloaxcin or dexamethasone in the serum or plasma of patients treated with Ciprodex® is undesirable. The drug, by the nature of its local application is meant to remain as such (within the ear canal or media). Drug concentration measurements were limited to plasma in an effort to determine the extent of systemic exposure to ciprofloxacin and dexamethasone following ototopical administration of Ciprodex®. The plasma levels however, are not associated with efficacy or response, but potentially toxicity. The sponsor did not assess the concentration of drug at the site of infection (i.e. otorrhea).

3. *What are the characteristics of the exposure response relationship (dose-response, concentration-response) for efficacy and safety?*

An exposure response relationship was not evaluated in this submission..

4. ***How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?***

The preparation of the drug is designed for topical application and therefore PK evaluation was essentially limited to determining the extent of drug absorption following local application. Evaluation of metabolites formed following absorption of ciprofloxacin and dexamethasone was not performed. Additionally, the absorption of ciprofloxacin and dexamethasone following application of Ciprodex® can only be evaluated in patients since the suspension is only effective at reaching the media of the ear when administered through a typanostomy tube. Thus a comparison to normal volunteers would not be possible. Concentrations of active metabolites were not measured dexamethasone. No active metabolites of ciprofloxacin exist. The plasma concentration of each drug is so low that determining any metabolites would be difficult.

5. ***What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?***

As expected the inter-subject variability of the primary PK parameter (C_{max}) was high for both ciprofloxacin and dexamethasone absorption. The % coefficient of variation for the maximal ciprofloxacin plasma concentration in nine patients treated with 8 drops of Ciprodex® (4 drops bilaterally) was 63.3%. The % coefficient of variation for maximal dexamethasone concentration in nine patients treated with 8 drops of Ciprodex® (4 drops bilaterally) was 135%. The cause of the variability may be influenced by several factors including the degree of inflammation at the site of infection and variable amounts of suspension reaching the media of the ear.

C. Intrinsic Factors

1. ***What intrinsic factors (age, gender, weight, height, disease, genetic polymorphism, pregnancy, organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?***

Ciprodex® is an ototopical preparation and any absorption would be considered undesirable. In general the mean concentrations of ciprofloxacin and dexamethasone in the plasma are low and not expected to result in any significant pharmacological or toxicological effect. Therefore the influence of intrinsic factors on exposure and subsequent response (in this case toxicity) to ciprofloxacin and dexamethasone would be of limited value.

D. Extrinsic Factors

1. ***What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?***

The influence of extrinsic factors on exposure (toxicity) has not been evaluated for Ciprodex®. Again the low plasma concentrations of both ciprofloxacin and dexamethasone achieved following ototopical administration would generally not warrant extrinsic factor influence studies (i.e. drug-drug interaction studies). The fact that the primary study population is pediatrics should preclude the need for evaluating the effect of smoking, alcohol and herbal product use on exposure (toxicity).

2. ***Based upon what is known about exposure-response relationships and their variability, what dosage adjustments, if any, do you recommend for each of these factors? If dose regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.***

There are no recommendations for dosage adjustment based on the local administration of Ciprodex® and minimal systemic absorption.

3. ***Drug-drug interactions***

In general the low plasma concentrations of ciprofloxacin and dexamethasone achieved following otic administration of Ciprodex® would not be expected to contribute to any significant drug-drug interactions.

E. General Biopharmaceutics

The route of Ciprodex® administration is ototopical therefore many of the general biopharmaceutics questions are not applicable.

F. Analytical Section

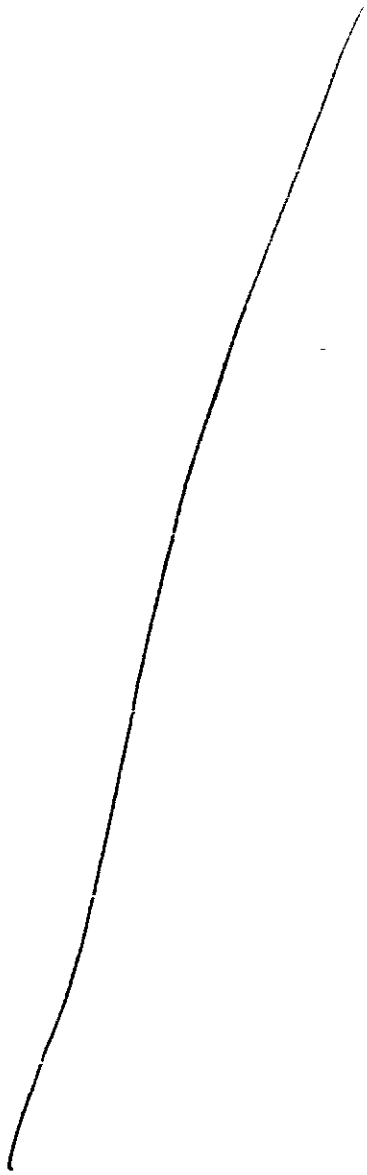
1. ***How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?***
Both ciprofloxacin and dexamethasone were identified and measured in the plasma via a validated LC/MS/MS method.

	Ciprofloxacin	*Dexamethasone*
Instrumentation		
Internal Standard		
Specificity		
Linearity		
Limit of Quantitation		
Stability in plasma		
Ambient temperature		
Freeze/thaw (–70° to ambient)		
Precision (% CV)		
Accuracy (% REC)		

APPEARS THIS WAY
ON ORIGINAL

V. Labeling Recommendations

Based on the exclusion of pharmacokinetic data obtained in study 00-68 from study site I, revision of the Clinical Pharmacology section is required to reflect the results of the pharmacokinetic study 02-58 conducted at study site II. This data includes 5 patients from the original pharmacokinetic study conducted at site II and 6 additional patients collectively grouped into study 02-58.



15 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

B. Individual Study Reviews

Title: Pharmacokinetic Analysis of Ciprofloxacin and Dexamethasome Following Administration of Ototopical CIPRODEX® Otic Suspension Using Data from Alcon Studies C-00-68 and C-02-58.

Location of Study Sites: [redacted]

Investigator: [redacted]

Protocol #s: C-00-68 and C-02-58

Objective: To evaluate the pharmacokinetic profile of ciprofloxacin and dexamethasone from a one-time bilateral ototopical administration of CIPRODEX® Otic in pediatric and young adult patients following tympanostomy tube surgery.

Methodology: Ciprofloxacin and dexamethasone pharmacokinetic data obtained from 11 pediatric patients who received CIPRODEX Otic Suspension (5 patients were from C-00-68, and 6 patients were from C-02-58). In both studies, the patients received a single, 4-drops/ear, ototopical, bilateral dose of CIPRODEX Otic Suspension immediately after tympanostomy tube insertion. Plasma samples were obtained between 5 and 30 minutes pre-dose; and, 15 and 30 minutes, and 1, 2, 4, and 6 hours post-dose. Drug concentrations for both studies were analyzed using the same validated LC/MS/MS methods at the same bioanalytical laboratory.

Study Drug Formulation: CIPRODEX® Otic suspension contains ciprofloxacin 0.3% (3mg/mL) and dexamethasone 0.1% (1mg/mL) in a sterile suspension of hydroxyethyl cellulose, tyloxapol, edetate disodium, sodium chloride, boric acid, acetic acid and purified water with a [redacted] The pH is adjusted to [redacted] with the addition of either sodium hydroxide or hydrochloric acid and the preparation contains 0.01% benzalkonium chloride as a preservative. CIPRODEX® otic was administered from a 5 mL DROP-TAINER® bottle, designed to deliver 35 µL of suspension per drop. Table 2 indicates the lot #s used in the pharmacokinetic evaluation.

Table 2

Study	Test Article	Lot Number	# of patients
C-00-68	CIPRODEX Otic Suspension	00-500126-1	5
C-02-58	CIPRODEX Otic Suspension	02-500406-1	6

Drug Dosing: The 5 patients from C-00-68 were randomized to CIRPODEX® Otic Suspension treatment, as this study was also intended to evaluate the pharmacokinetics of ciprofloxacin following otic administration of Ciloxan® solution. All patients intraoperatively, received 4 drops of CIPRODEX® bilaterally following surgical insertion of typanostomy tubes. The 6 patients enrolled in study C-02-58 were treated identical to patients receiving CIPRODEX® Otic in study C-00-68. Patients treated in both studies received a dose of ciprofloxacin and dexmethasone equal to 840 µg and 280 µg, respectively immediately following insertion of typanostomy tubes.

Blood sampling time points for PK analysis: Blood samples were obtained at 5 and 30 minutes pre-dosing then at 0.25, 0.5, 1.0, 2.0, 4.0 and 6.0 hours post-dosing.

Analytical Assay:

Analytical site: [redacted]

Whitesboro, NY 13492

Table 3. Summary of Ciprofloxacin and Dexamethasone Analytical Method Validation in Plasma

	Ciprofloxacin	*Dexamethasone*
Instrumentation		
Internal Standard		
Specificity		
Linearity		
Limit of Quantitation		
Stability in plasma		
Ambient temperature		
Freeze/thaw (–70° to ambient)		
Precision (% CV)		
Accuracy (% REC)		

Pharmacokinetic analysis: The plasma drug pharmacokinetic parameters for ciprofloxacin and dexamethasone were estimated by model independent methods (Model 200, WinNonlin Enterprise, Version 3, Pharsight Corporation, Mountain View, California). When plasma concentrations of ciprofloxacin and/or dextamethasone were quantifiable in plasma, the pharmacokinetic parameters assessed included the plasma drug concentrations at each sampling time, C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$. C_{max} and T_{max} were observed values.

Statistical analysis: Descriptive statistics (mean, standard deviation, N, minimum, and maximum) and 95% confidence limits were provided for plasma concentrations of ciprofloxacin and dexamethasone for each sample time. When available, single dose estimates for C_{max}, T_{max}, AUC_{0-t}, $AUC_{0-\infty}$, and $t_{1/2}$ were described, similarly based on the plasma concentrations.

Results: 11 patients were included in the combined studies (C-00-68 and C-02-58). Patient #205 from study C-00-68 demonstrated a substantial dexamethasone concentration in the baseline sample. Approximately, 1.2 µg/mL dexamethasone was detected in the baseline plasma sample, indicating that this patient was treated with IV dexamethasone during the surgical procedure. As a result patient #205 should be excluded from PK analysis based on inclusion and exclusion criteria established by the Sponsor. Additionally, patient #207 also from study C-00-68 demonstrated quantifiable concentrations of ciprofloxacin and dexamethasone at 0.25 and 0.5 hours post-dosing, however, samples were not available after this time point. Ototopical administration of CIPRODEX® appears to result in relatively consistent ciprofloxacin T_{max} values at approximately one to two hours' post administration. Conversely, dexamethasone T_{max} values were considerably more variable, therefore, the true extent of exposure to either ciprofloxacin or dexamethasone in this patient are unclear.

For the purposes of data analysis as it relates to PK, patient #207 will be included in the analysis of ciprofloxacin exposure and excluded from the analysis of dexamethasone exposure. This patient appears to have received a pre- CIPRODEX® IV dose of dexamethasone judging by the baseline plasma sample concentration of dexamethasone.

Note: This patient, as stated in the inclusion/exclusion criteria previously defined by the investigator, should have been identified as receiving IV dexamethasone and not subjected to blood sampling for the PK study.

Nine of the eleven patients demonstrated plasma ciprofloxcin concentrations above the limit of quantitation following bilateral ototopical dosing. While, nine of ten evaluable patients demonstrated plasma dexamethasone concentrations above the limit of quantitation.

Tables 4 and 5 illustrate individual patient plasma concentrations of ciprofloxacin and dexamethasone, respectively.

Tables 6 and 7 illustrate individual patient PK parameters for ciprofloxacin and dexamethasone, respectively.

Figures 1-8 show graphical representations of PK parameters for individual and mean patient data.

Table 4

Individual and Mean (SD) Ciprofloxacin Plasma Concentrations After a Single Bilateral Ototopical Dose of 4 Drops/Ear of CIPRODEX Otic Suspension in Pediatric Patients Undergoing Tympanostomy Surgery.

Patient#/ Study #	Plasma Concentrations (ng/mL) Following Dosing						
	0 hours	0.25 hours	0.5 hours	1 hour	2 hours	4 hours	6 hours
201/00-68							
202/00-68							
205/00-68							
207/00-68							
209/00-68							
201/02-58							
202/02-58							
203/02-58							
204/02-58							
205/02-58							
206/02-58							
Mean	---	**1.26**	**1.27**	**1.35**	**1.33**	**0.800**	**0.585**
SD	---	**0.823**	**0.822**	**0.967**	**0.695**	**0.175**	---
N	---	**8**	**8**	**7**	**7**	**6**	**2**
[Min.]	---						
[Max.]	---						

Table 5

Individual and Mean (SD) Dexamethasone Plasma Concentrations After a Single Bilateral Ototopical Dose of 4 Drops/Ear of CIPRODEX Otic Suspension in Pediatric Patients Undergoing Tympanostomy Surgery.

Patient#/ Study #	Plasma Concentrations (ng/mL) Following Dosing						
	0 hours	0.25 hours	0.5 hours	1 hour	2 hours	4 hours	6 hours
201/00-68							
202/00-68							
205/00-68							
207/00-68							
209/00-68							
201/02-58							
202/02-58							
203/02-58							
204/02-58							
205/02-58							
206/02-58							
Mean	---	**0.929**	**0.800**	**0.823**	**0.749**	**0.470**	**0.332**
SD	---	**1.59**	**1.03**	**0.791**	**0.598**	**0.378**	**0.228**
N	---	**9**	**9**	**7**	**8**	**8**	**5**
[Min.]	---						
[Max.]	---						

BLQ (Below limit of quantitation), IV (Intra-venous dose prior to ototopical administration), NS (No available sample)

Table 6

Individual and Mean (SD) Pharmacokinetic Parameters for Ciprofloxacin After a Single Bilateral Ototopical Dose of 4 Drops/Ear of CIPRODEX Otic Suspension in Pediatric Patients Undergoing Tympanostomy Surgery.

Patient #	Study #	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-4} (ng * h/mL)	AUC_{0-6} (ng * h/mL)
201	C-00-68				
202	C-00-68				
205	C-00-68				
207	C-00-68				
209	C-00-68				
201	C-02-58				
202	C-02-58				
203	C-02-58				
204	C-02-58				
205	C-02-58				
206	C-02-58				
Mean		**1.39**	**1.32**	4.96	8.53
SD		**0.880**	**0.814**	2.30	---
N		9	9	6	2
Min					
Max					

Table 7

Individual and Mean (SD) Pharmacokinetic Parameters for Dexamethasone After a Single Bilateral Ototopical Dose of 4 Drops/Ear of CIPRODEX Otic Suspension in Pediatric Patients Undergoing Tympanostomy Surgery.

Patient #	Study #	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-4} (ng * h/mL)	AUC_{0-6} (ng * h/mL)
201	C-00-68				
202	C-00-68				
205	C-00-68				
207	C-00-68				
209	C-00-68				
201	C-02-58				
202	C-02-58				
203	C-02-58				
204	C-02-58				
205	C-02-58				
206	C-02-58				
Mean		**1.14**	**1.32**	2.64	4.94
SD		**1.54**	**0.83**	2.53	2.95
N		**9**	**9**	8	5
Min					
Max					

NA (Not applicable), ND (Not determined)

Figure 1. Individual Patient Plasma Ciprofloxacin Concentration - Time Profiles

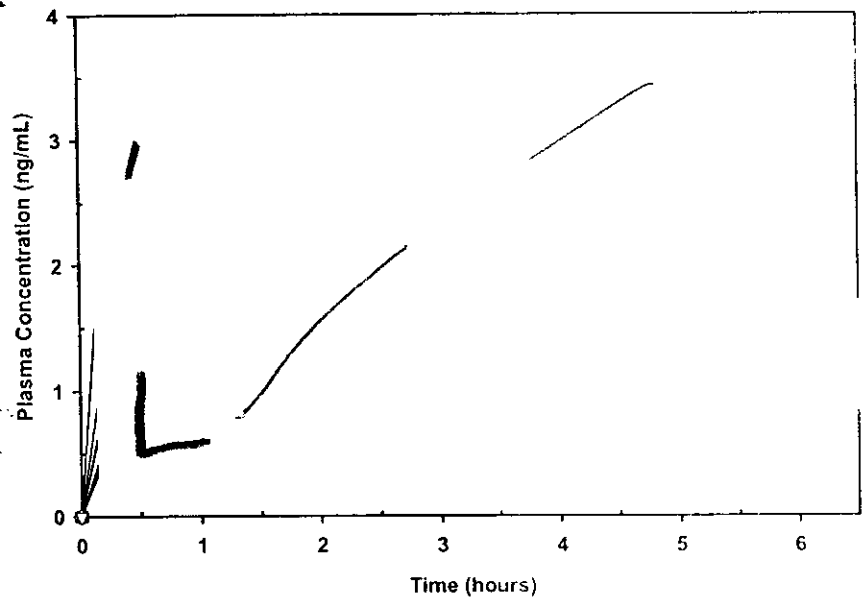


Figure 2. Mean (SD) Plasma Ciprofloxacin Concentration - Time Profile

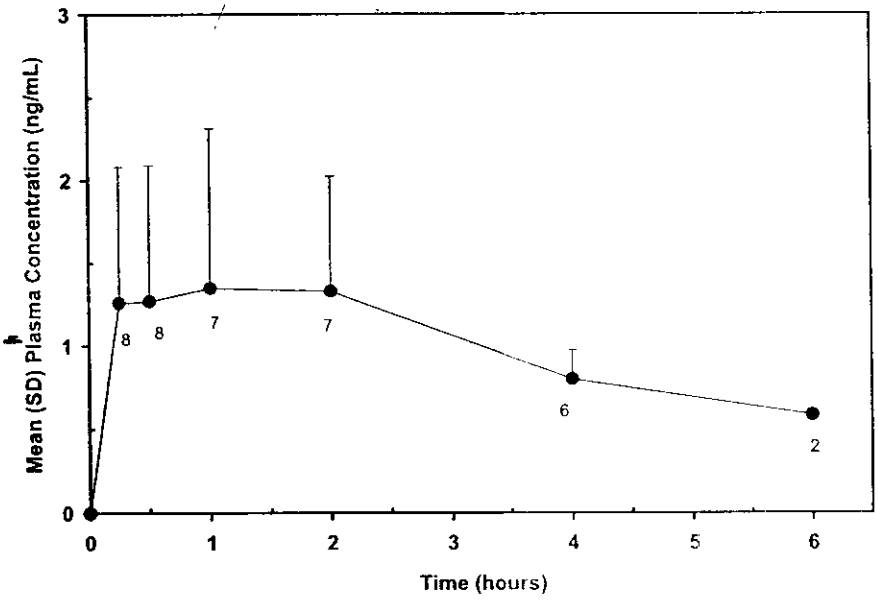


Figure 3. Individual Patient Dexamethasone Plasma Concentration - Time Profiles
(Including Patient 206 / Study 02-58)

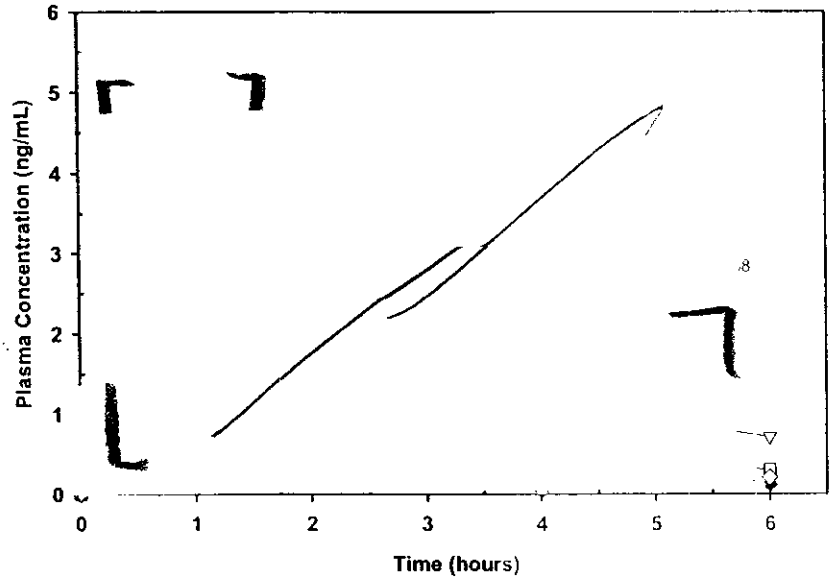


Figure 4. Individual Patient Dexamethasone Plasma Concentration - Time Profiles
(Excluding Patient 206 / Study 02-58)

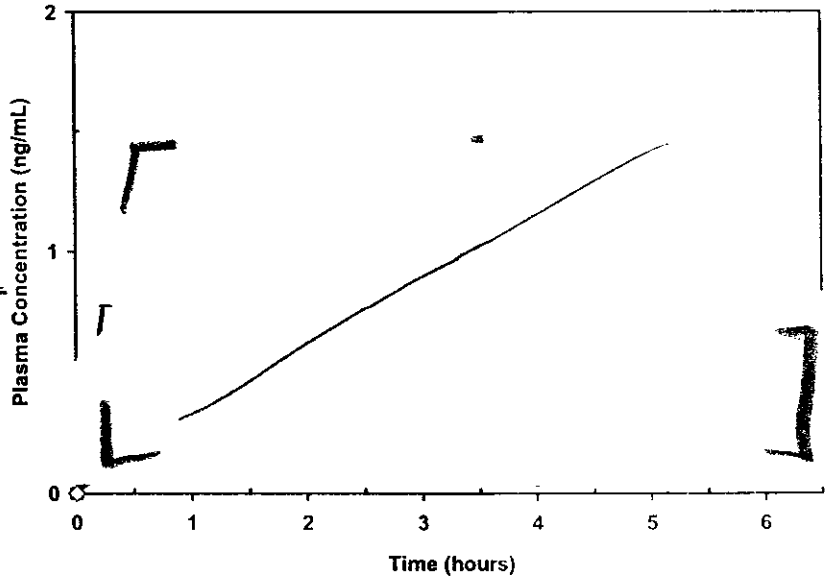


Figure 5. Mean (SD) Plasma Dexamethasone Concentration - Time Profile (Including Patient 206 / Study 02-58)

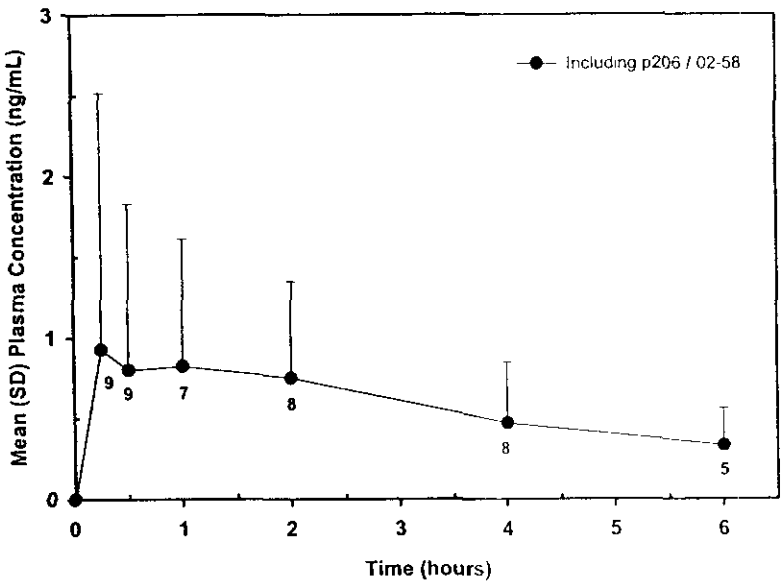


Figure 6. Mean (SD) Dexamethasone Concentration - Time Profile (Excluding Patient 206 / Study 02-58)

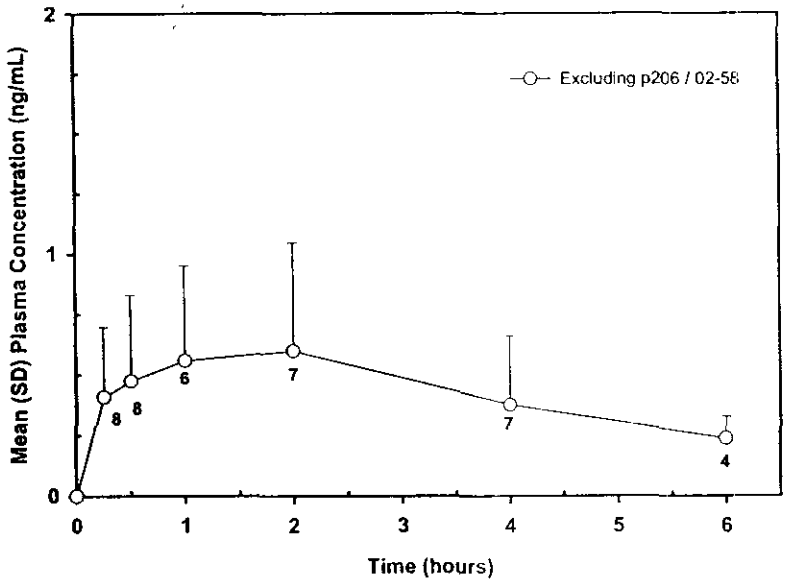


Figure 7. Maximal Individual Patient Ciprofloxacin Plasma Concentrations

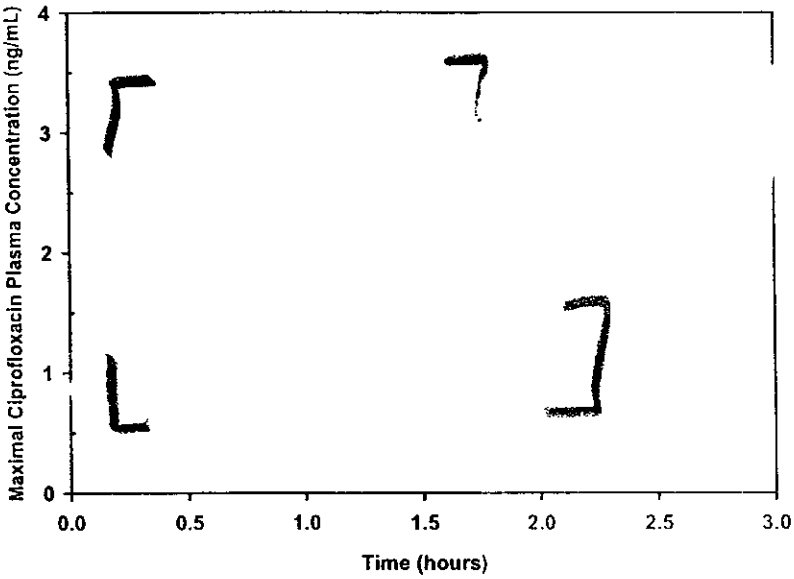
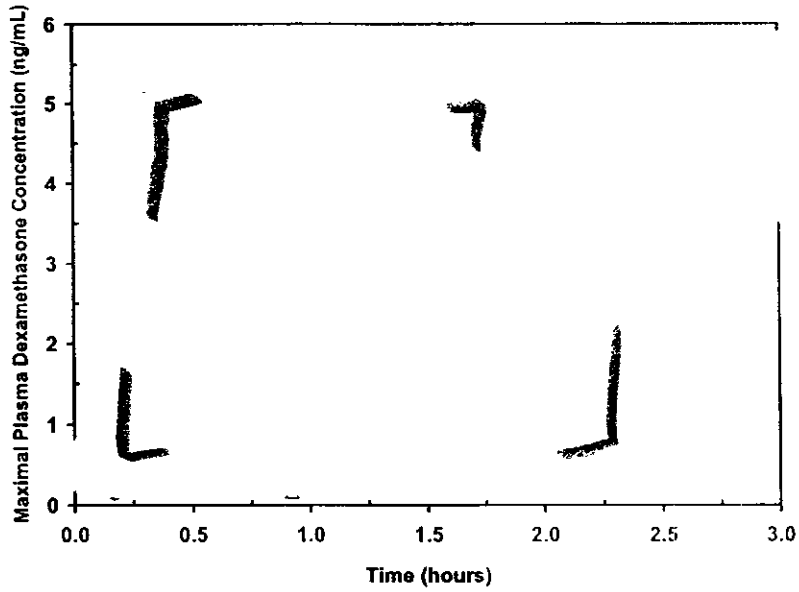


Figure 8. Maximal Individual Patient Dexamethasone Plasma Concentrations



Conclusions:
The absorption of ciprofloxacin following ototopical administration of 8 drops (4 drops bilaterally) of Ciprodex® was observed in 9 of 11 patients. The mean (± SD) peak plasma concentration of ciprofloxacin was 1.39 ± 0.88 ng/mL (range. — ng/mL). 2 of the 9 patients displayed quantifiable plasma concentrations (≥ 0.50 ng/mL) at 6 hours post administration. The absorption of dexamethasone following ototopical administration of 8 drops (4 drops bilaterally) of Ciprodex® was observed in 9 of 10 patients. The mean (± SD) peak plasma concentration of dexamethasone was 1.14 ± 1.54 ng/mL (range: — — ng/mL). 5 of the 9 patients displayed quantifiable plasma concentrations (> — ng/mL) at 6 hours post administration.

Peak plasma concentrations for ciprofloxacin following 4 drops Ciprodex bilaterally (total dose = 0.840 mg ciprofloxacin) were approximately 0.1% of peak concentrations following a 250 mg tablet oral dose. Minimal accumulation of drug over time would be expected based on the plasma concentrations at 6 hours post dosing BLQ in most (7/9) patients. Peak plasma concentrations of dexamethasone following 4 drops of Ciprodex bilaterally (total dose = 0.280 mg dexamethasone) were approximately 14% of the peak concentration resulting from a 0.5 mg oral tablet dose. While HPA axis suppression was not evaluated for the purposes of this submission, the dexamethasone concentrations observed would not be expected to create suppression of the HPA axis. Blood sampling was not performed for the duration of a typical treatment regime (i.e. 7 days) therefore; accumulation of the drug is unknown. Based on the low and variable plasma concentrations (0.332 ± 0.228 ng/mL) in the 5 patients demonstrating quantifiable dexamethasone concentrations at 6 hours post dosing, significant accumulation over the seven day treatment period would not be expected. Additionally, prediction of dexamethasone accumulation would be difficult to simulate based on variability of absorption from dose to dose.

Peak concentrations of dexamethasone following a 0.5-mg oral dose in healthy adult women created a 24% depression in cortisol levels 24 hours after dosing. This corresponded with a peak plasma concentration of → ng/mL. It is accepted that dexamethasone peak concentration is the PK parameter that affects the HPA axis. It would appear from the current study that concentrations of dexamethasone absorbed following ototopical dosing would not reach clinically relevant concentrations over a 7 day period.

Patient # 206/C-02-58 displayed greater than expected plasma concentrations of dexamethasone. The plasma concentration-time profile appears as if the patient received an IV dose of dexamethasone at some point. However, no records exist to establish that this patient received IV dexamethasone and no concentration of dexamethasone was reported in the pre Ciprodex® dosing baseline. Therefore, no documentation exists to warrant excluding this patient from the PK analysis.

Comments:
(1) The Sponsor should provide valid information regarding patient #206/C-02-58 which would support removal from analysis. Absorption appears to support the Sponsor's claim that the patient may have received a small IV dose of dexamethasone, however, systemic absorption following ototopical administration is highly variable and without documentation of the patient meeting the exclusion criteria of the study (in this case IV dexamethasone administration) the patient's data must be included.
(2) The peak concentrations for ciprofloxacin and dexamethasone (mean ± SD) were recalculated using only patients that demonstrated quantifiable plasma concentrations. Thus the number of patients was equal to 9 rather than 11.
(3) Determining $AUC_{0-\infty}$ and terminal half-life values from the data obtained is incorrect in the opinion of the reviewer. Replacing plasma samples demonstrating concentrations below the limit of quantitation (LOQ) with ½ the LOQ value will provide misleading results. When these patients are removed from the analysis we find that 2 patients demonstrate quantifiable ciprofloxacin concentrations at the final time point and 5 patients demonstrate quantifiable dexamethasone concentrations. $AUC_{Clast-\infty}$ values

account for approximately 25% of the total $AUC_{0-\infty}$, therefore the utility of reporting terminal half-lives for ciprofloxacin and dexamethasone in the label may be misinterpreted.

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Paul Buehler
7/17/03 02:03:28 PM
BIOPHARMACEUTICS

Phil Colangelo
7/18/03 04:30:29 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL