CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-537

PHARMACOLOGY REVIEW(S)

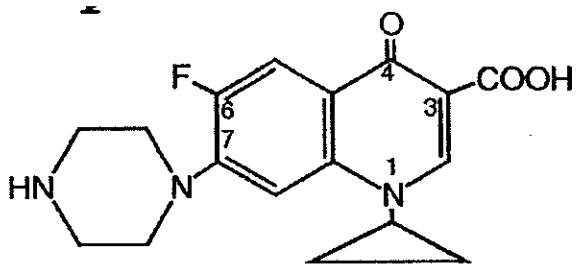
PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21,537
Review number: 1
Sequence number/date/type of submission: 000; 9/30/02; original NDA submission
Information to sponsor: Yes (X)- [labeling changes] No ( )
Sponsor and/or agent: Alcon, Inc.; Fort Worth, TX
Manufacturer for drug substance: Ciprofloxacin will be manufactured by Bayer; Dexamethasone will be manufactured by [redacted]

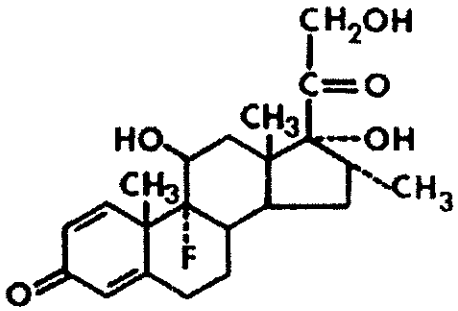
Reviewer name: Amy L. Ellis
Division name: Anti-Infective Drug Products
HFD #: 520
Review completion date: 6/17/03

Drug:

Trade name: Ciprodex®
Generic name (list alphabetically): 0.3% ciprofloxacin/0.1% dexamethasone
Code name: none
Chemical name: Ciprofloxacin is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Dexamethasone is 9-fluoro-11β, 17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione.
Molecular formula/molecular weight: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$, [redacted] (ciprofloxacin); $C_{22}H_{29}FO_5$, [redacted] (dexamethasone)
Structures:



Ciprofloxacin



Dexamethasone

Relevant INDs/NDAs/DMFs: IND 54,670

Drug class: Fluoroquinolone antimicrobial with synthetic corticosteroid

Indications: Acute otitis media [redacted] in patients ≥ 6 months of age with tympanostomy tubes; Acute otitis externa in patients ≥ 6 months of age

Clinical formulation:

Ciprofloxacin Hydrochloride	[redacted]
Dexamethasone	0.1%
Benzalkonium Chloride	[redacted]
Hydroxyethyl Cellulose	
Sodium Acetate	
Acetic Acid	
Sodium Chloride	
Edetate Disodium	
Tyloxapol	
Boric Acid	
NaOH	adjust pH
HCl	adjust pH
Purified Water	

Route of administration: ototopical

Proposed use: Treatment of acute otitis media with tympanostomy tubes and acute otitis externa

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

Executive Summary

I. Recommendations

A. Recommendation on Approvability: The pharmacologist has no objection to the approval of this NDA.

B. Recommendation for Nonclinical Studies: None.

C. Recommendations on Labeling: Revisions are needed to make the label for Ciprodex® consistent with the label for Cipro® HC Otic.

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Ciprodex® or its vehicle caused irritation to the middle ear tissues of guinea pigs when administered intratympanically. Mild low frequency hearing loss experienced by some animals appeared to be associated with a loss of conduction secondary to tissue irritation. This has also been observed with Cipro® HC Otic Suspension. No damage to cochlear hair cells was associated with ciprofloxacin and/or dexamethasone in the initial 28 day guinea pig ototoxicity study conducted with Ciprodex®, also consistent with studies conducted with Cipro® HC Otic Suspension. In contrast, outer hair cell loss in the basal region of the cochlea was observed in cytocochleograms from 2/10 guinea pigs per group in a subsequent 14 day where the animals were dosed with Ciprodex® (with or without degradation products). Considering the totality of the data, the pharmacology reviewer does not consider it likely that ciprofloxacin or dexamethasone would be toxic to cochlear hair cells if a small amount entered the middle ear through a rupture in the tympanic membrane. Ciprodex® did not induce sensitization in the guinea pig when a dermal challenge followed topical induction.

B. Pharmacologic Activity: Ciprofloxacin interferes with the enzyme DNA gyrase and inhibits DNA synthesis in susceptible bacteria. Dexamethasone inhibits the inflammatory process.

C. Nonclinical Safety Issues Relevant to Clinical Use: Nothing apparent.

III. Administrative

A. Reviewer signature: _____

B. Supervisor signature: Concurrence (TL)- _____

Concurrence (Deputy Div Dir)- _____

Non-Concurrence - _____
(see memo attached)

cc: list:

PM/Nguyen
MO/Smith
Chem/Sloan
Micro/Silver
Stat/Jiang
Biopharm/Buehler

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Ciprofloxacin interferes with the enzyme DNA gyrase and inhibits DNA synthesis in susceptible bacteria. Dexamethasone inhibits the inflammatory process.

II. SAFETY PHARMACOLOGY:

No safety pharmacology studies were performed with Ciprodex® Otic Suspension and none were necessary.

III. PHARMACOKINETICS/TOXICOKINETICS:

No pharmacokinetic or toxicokinetic studies were performed with Ciprodex® Otic Suspension in animals and none were necessary. Each dose of Ciprodex® contains relatively small amounts of ciprofloxacin and dexamethasone. Four drops, 0.14 ml, are instilled twice daily into each affected ear. This is equivalent to 0.42 mg of ciprofloxacin and 0.14 mg of dexamethasone per dose, or up to 1.68 mg of ciprofloxacin and 0.56 mg of dexamethasone per day if both ears are being treated. Studies conducted by the sponsor in human pediatric patients with tympanostomy tubes demonstrated that absorption of ciprofloxacin (mean Cmax 1.55 ng/ml, 0.25-2 hr after dosing) and dexamethasone (Cmax – .g/ml, 0.17-2.1 hr after dosing) occurred following otic administration. The distribution, metabolism, and excretion of both drugs have been studied previously in animals and humans to support their uses as an antimicrobial (systemic and ophthalmic) and a corticosteroid anti-inflammatory (systemic, topical, ophthalmic). The sponsor submitted a reference from the literature (Bagger-Sjoback, et al., J Otorhinolaryngol 54(1): 5-9, 1992) suggesting that ciprofloxacin can be absorbed through the round window membrane of chinchillas when directly applied to it.

IV. GENERAL TOXICOLOGY:

General toxicity studies were not conducted with Ciprodex®. Ototoxicity (intratympanic dosing) and dermal sensitization studies were conducted in guinea pigs to support clinical use of the drug product.

V. GENETIC TOXICOLOGY:

No new genetic toxicology studies were submitted for either ciprofloxacin or dexamethasone and none were necessary. This section of the label will be consistent with labels for other products that contain ciprofloxacin or dexamethasone. *In vitro*, ciprofloxacin was negative in the Ames *Salmonella* reversion assay, an *E. coli* DNA repair assay, the Chinese Hamster V_{79} Cell HGPRT test, the Syrian Hamster Embryo (SHE) Cell transformation assay, *Saccharomyces cerevisiae* point mutation assay, and *Saccharomyces cerevisiae* mitotic crossover and gene conversion assay. It was, however, positive in the Mouse Lymphoma Cell forward mutation assay and the rat hepatocyte DNA repair assay. *In vivo*, ciprofloxacin was negative in

the rat hepatocyte DNA repair assay, a mouse micronucleus test, and a dominant lethal test also conducted in mice.

The sponsor provided a reference (Singh et al, Mutation Research 308: 89-97, 1994) describing several genetic toxicology studies conducted with dexamethasone. *In vitro*, the Ames *Salmonella* reversion assay was negative, but dexamethasone induced sister chromatid exchange and chromosome aberrations in cultured human lymphocytes. *In vivo*, a mouse micronucleus test was positive and dexamethasone also induced sister chromatid exchange in mouse bone marrow cells.

VI. CARCINOGENICITY:

Two year bioassays conducted in rodents using daily oral doses of ciprofloxacin up to 750 mg/kg (mice) and 250 mg/kg (rats) revealed no evidence of carcinogenesis. Carcinogenicity studies have not been conducted with dexamethasone. No long term studies of Ciprodex® Otic Suspension were performed to evaluate its carcinogenic potential.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Reproductive and developmental toxicity studies have not been performed with Ciprodex® Otic Suspension. To be consistent with other otic products containing fluoroquinolones with or without corticosteroids, the same information and Pregnancy Category that is given for the relevant systemic products will be provided in the label for Ciprodex® Otic Suspension. The amount of ciprofloxacin that can be delivered by ototopical administration is unlikely to cause any effects on fertility or on the developing embryo or fetus. Corticosteroids are generally teratogenic in laboratory animals when they are administered systemically at relatively low dose levels and the more potent of these compounds are animal teratogens even when dermal or ophthalmic routes of administration are used.

Oral doses of ciprofloxacin up to 100 mg/kg/day were not associated with impairment of fertility in rats. Ciprofloxacin was not teratogenic or embryotoxic to rats or mice after administration of maternal oral doses up to 100 mg/kg or IV doses up to 30 mg/kg. In rabbits, oral doses $\geq$30 mg/kg were associated with gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but not teratogenicity. Maternal toxicity was not observed in rabbits given IV doses of ciprofloxacin $\leq$20 mg/kg and neither embryotoxicity or teratogenicity was observed in the offspring. These sort of findings in rabbits are common to many antimicrobial drug products.

Dermal application of dexamethasone to male rats at a dose of 1.8 mg/kg for 26 weeks was associated with changes in the male reproductive organs including testes, epididymides, sperm ducts, prostate, seminal vesicles, Cowper's gland, and accessory glands (the sponsor found this information in the Registry of Toxic Effects of Chemical Substances [RTECS] No. TU3980000). These changes, which could have an impact on fertility, are not likely to be relevant to short-term ototopical use of Ciprodex® Otic suspension. The RTECS information also includes citations for numerous animal studies where abnormal fetal development has been observed following maternal treatment with dexamethasone using various routes of administration including topical. The sponsor also cites a publication (Kasirsky and Lombari, Tox Appl Pharm 16: 773-778, 1970) describing a study where pregnant New Zealand White

rabbits were treated with corticosteroids several times daily via an ophthalmic route of administration during organogenesis. Although the sponsor has cited this information in the labels for their Tobradex® ophthalmic products, the study is relatively old and the quality of the methodology is unknown. Additionally, there were only 10 pregnant rabbits in each treatment group with half sacrificed on day 29 of gestation and the other half allowed to deliver their offspring before sacrifice. Dexamethasone (0.1%) was associated with an increase in abnormalities that were confined primarily to the abdominal cavity. These included kidney hypoplasia, "intestinal disorders" (including absence of intestines), and herniated abdominal viscera. The untreated or saline-treated controls had overall incidences of fetal anomalies below 1%, with average maternal and fetal weights that were higher than those for the drug treated does and fetuses. The overall incidences of malformed fetuses in the 2 dexamethasone groups were 32.3% (term) and 15.6% (day 29). Despite the fact that these rabbit data have been included in the labels of the sponsor's ophthalmic products that contain dexamethasone, the pharmacologist is not convinced that the information is of a high enough quality to merit being included in the label and recommends using categorical language regarding corticosteroid effects on reproduction similar to that found in the label for Cipro® HC otic suspension.

VIII. SPECIAL TOXICOLOGY STUDIES:

Ototoxicity Study with Ciprofloxacin/Dexamethasone Otic Suspension with Degradation Product in the Guinea Pig (Technical Report No. 056:30:602; Protocol No. N-01-249; Study No. TO-0102)

[redacted]), LE Lemke

(Alcon, Fort Worth, TX)

Report dated 8/26/02, U.S. GLP (except that animals were not housed in a facility that followed GLP though it was AAALAC accredited)

Animals: Male (277-410 g) and female (287-380 g) NIH pigmented guinea pigs [redacted], young adults (19-32 days old); 5/gender were assigned to the ciprofloxacin/dexamethasone and vehicle groups and 3/gender were assigned to the neomycin and saline groups. Animals were unilaterally implanted with a cannula to the middle ear, proceeding from the bulla and terminating in the niche above the round window membrane. Surgery was not performed on all animals on the same day, but an attempt was made to implant at least one guinea pig per dose group on each surgery day as group size allowed.

Diet: [redacted] and tap water were available *ad libitum*.

Drug Dose and Route of Administration: The animals were divided into 5 groups, 0.3% ciprofloxacin/0.1% dexamethasone suspension (Lot No. 00-26420-6), 0.3% ciprofloxacin/ 0.1% dexamethasone suspension with degradation products (Lot No. 01-30293-2), vehicle (Lot 01-30289-2), 0.9% sodium chloride (negative control), and 10% neomycin sulfate (positive control). Each day at approximately 9 a.m. and 5 p.m., 10 µl of the appropriate test substance was introduced into the middle ear via a surgically implanted catheter that terminated in the niche

above the round window membrane. All test solutions and suspensions were supplied by the sponsor and stored at room temperature. The degradation products found in the test article were as follows (expressed as a percentage of active ingredients):

Length and Conduct of Study: The animals were treated with drug twice daily for 14 days. Drug treatment commenced on the day following cannula implantation (Day 0). Guinea pigs were observed each day for clinical signs of toxicity and weighed at the beginning and end of the dosing period. Auditory brainstem response (ABR) was measured in each animal prior to the implantation of a drug delivery catheter and again before termination on Day 14. The frequencies used for ABR evaluation were 2, 8, and 16 kHz. Cochleae were locally perfused with fixative (4% paraformaldehyde in phosphate buffer) after animals were beheaded. These organs were then immersed in fixative overnight and later dissected and stained with rhodamine fluorescent-labeled phalloidin prior to photomicroscopic examination of hair cells under epifluorescent illumination. The middle ear tissues were examined using a dissection microscope.

Results: No clinical signs of toxicity were observed and all guinea pigs survived until the end of the study. Body weight gain was similar between dose groups.

The variability of the baseline ABR thresholds (measured prior to surgical placement of the dosing catheters) was similar between guinea pigs assigned to the different treatment groups at each frequency tested.

ABR Thresholds (dB, Mean ± SD; Range) in Guinea Pigs Prior to Treatment

Treatment Group	2 kHz	8 kHz	16 kHz
Saline Control	35.5 ± 5.9	16.5 ± 6.7	23.8 ± 3.7
Vehicle Control	38.8 ± 7.4	16.8 ± 6.6	21.4 ± 3.7
0.3% Cipro/0.1% Dex	39.5 ± 7.4	16.8 ± 4.9	21.7 ± 4.2
1% Cipro/0.3% Dex + degradation prod	39.5 ± 3.3	16.3 ± 3.0	20.7 ± 5.1
Neomycin	34.0 ± 4.4	14.7 ± 3.0	21.0 ± 4.5

Changes in ABR Threshold (dB) Following 14 Days of Intratympanic Dosing of Test Substances (Mean ± SD; Range)*

Treatment Group	2 kHz	8 kHz	16 kHz
Saline Control	7.3 ± 11.8	4.0 ± 15.5	4.8 ± 20.9
Vehicle Control	18.5 ± 18.8	13.4 ± 10.4	7.9 ± 10.3
0.3% Cipro/0.1% Dex	12.7 ± 15.8	18.9 ± 21.4	12.1 ± 18.5
1% Cipro/0.3% Dex + degradation prods	19.4 ± 22.5	18.4 ± 13.0	19.2 ± 20.5
Neomycin	40.5 ± 6.4	39.0 ± 10.4	46.7 ± 10.5

*An increase in the ABR threshold would correspond with a decrease in hearing at the particular frequency tested.

Average ABR thresholds in the vehicle or Ciprodex® groups did not differ significantly from saline controls after 14 days of treatment. Average ABR thresholds for the neomycin group were significantly higher than saline controls at each frequency tested (p values $\leq$0.002).

Each animal in the neomycin group experienced severe losses of both inner and outer cochlear hair cells, particularly in the basal region, though several guinea pigs treated with this compound experienced hair cell loss throughout the cochlea. Moderate to severe hearing loss as measured by the ABR was apparent in all animals at each test frequency. In general, the appearance of the middle ear in these animals was normal except for slight to moderate thickening of the mucosa in about half of the neomycin-treated guinea pigs.

In the saline control group, one guinea pig had a middle ear infection and fibrous tissue was present in the middle ear. This animal had hearing loss at all 3 frequencies (31, 28, and 46 dB at 2, 8, and 16 kHz, respectively), but no cochlear hair cell loss. Two guinea pigs in the vehicle group that had middle ear infections did not experience comparable hearing losses- one of these animals had an ABR threshold increase of 38 dB at 2 kHz, but other frequencies were within 20 dB of baseline. Two other animals in the vehicle group experienced an ABR threshold elevation greater than 30 dB. Both of these occurred at 2 kHz (44 and 39 dB). Another guinea pig had an ABR threshold increase of 29 dB at 2 kHz and a 26 dB increase at 16 kHz. No other animals in the vehicle group had an ABR threshold increase > 21 dB at 16 kHz. Cytocochleograms were normal for all of the vehicle treated animals, so the modest low frequency hearing losses were probably due to a loss of conduction secondary to middle ear changes (e.g., irritation, deposits).

In the ciprofloxacin/dexamethasone groups, 2 guinea pigs from each group (with and without degradation products) had ABR threshold elevations >25 dB at all 3 frequencies tested. In the group without degradation products, the ABR elevations at 2, 8, and 16 kHz were 34, 57, and 48 dB, and 26, 49, and 41 dB. In the group with degradation products, these values were 38, 37, and 59, and 41, 27, and 53. All 4 of these animals showed a loss of outer (but not inner) hair cells from the basal portion of the cochlea, the area associated with high frequency hearing capacity. No other guinea pigs in these groups had an ABR threshold increase >20 dB at 16 kHz. One animal in the Ciprodex® group without degradation products had ABR threshold increases

of 33 and 32 dB at 2 and 8 kHz and one in the group with degradation products had increases of 60 and 26 dB at these frequencies. The remaining guinea pigs had ABR changes within 30 dB of baseline; most were less than 25 dB.

Examination of the middle ear using a dissecting microscope revealed clumps of white granular or crystalline material in most of the guinea pigs that were treated with Ciprodex®, with or without degradation products. The investigators speculate that it was precipitated drug since it was not present in the other groups. Five animals from the vehicle group and 1 from the saline group had a white layer (up to 1 mm thick) of "soft porous material lining the middle ear surface of the bulla bone." The report stated that it "resembled extracellular material mixed with amorphous connective tissue." This material was not present in any ears of the Ciprodex® or neomycin groups; the investigators believed that the drugs may have suppressed its formation. Slight to severe thickening of the middle ear mucosa and possible compromise of ossicular movement were seen in most animals from the Ciprodex® and vehicle groups and slight to severe bulla bone thickening was observed in several animals from each of these groups. While middle ear changes did not strictly correlate with the low frequency hearing losses seen in a number of these guinea pigs, they appeared to be a contributing factor and there was a general association between the two.

The presence of degradation products in the Ciprodex® suspension did not increase ototoxicity. In contrast to an earlier study with Ciprodex® suspension, outer hair cell loss in the basal region of the cochlea was observed in cytocochleograms from some guinea pigs that were treated with the product. Considering the totality of the data, the pharmacology reviewer does not believe that ciprofloxacin or dexamethasone is likely to be toxic to cochlear hair cells if a small amount enters the middle ear through a rupture in the tympanic membrane. The investigators believed that back pressure on the dosing syringe could have damaged the round window membrane of some animals, allowing greater amounts of Ciprodex® to reach the interior of the cochlea, but there is no direct evidence that this occurred because round window membrane ruptures are known to be quickly repaired and difficult to detect. Additionally, back pressure occurred during the dosing of some animals that had no loss of cochlear hair cells. Irritation of the middle ear mucosa was observed in guinea pigs treated with Ciprodex® suspension or vehicle, consistent with observations from previous studies.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Although studies in humans and animals indicate that ciprofloxacin and dexamethasone can be absorbed following otic administration, only low systemic levels are present. A total of 0.84 mg of ciprofloxacin and 0.28 mg of dexamethasone would be administered daily into each affected ear if dosage instructions were followed.

Ciprodex® Otic Suspension did not induce sensitization in guinea pigs following a topical dermal challenge after topical induction.

Intratympanic administration of 0.3% ciprofloxacin/0.1% dexamethasone suspension, 1% ciprofloxacin/0.3% dexamethasone suspension, or 0.3 % ciprofloxacin solution to guinea pigs twice daily for 28 days did not appear to be ototoxic. Ciprofloxacin was not associated with cochlear hair cell damage or changes in the ossicles. The slight to moderate increases in Auditory Brainstem Response (ABR) thresholds observed in drug-treated animals at some

frequencies (particularly the lower ones) may have been due to decreased conduction secondary to the presence of drug residue in the middle ear or irritation of tissues of the middle ear. Previous studies with ciprofloxacin and other fluoroquinolones (using concentrations of drug similar to the amount of ciprofloxacin present in the current product) have not demonstrated cochlear hair cell damage. Middle ear irritation has been observed with intratympanic dosing of several compounds. When a second guinea pig ototoxicity study was conducted using Ciprodex® Otic Suspension ± degradation products, outer hair cell loss in the basal region of the cochlea was observed in a few guinea pigs from both Ciprodex® groups and these animals also experienced moderate high frequency hearing loss as assessed by ABR. The presence of the degradation products was not associated with an increase in ototoxicity. The degree of hair cell loss was not as great as that observed with the positive control, neomycin. Although the reasons for the differences between these 2 Ciprodex® guinea pig studies are not clear, the totality of the data with ciprofloxacin do not appear to indict this compound as an ototoxicant. It is important to consider that the dosing procedure used in the guinea pig studies maximizes middle ear (and likely inner ear) exposure to the test compounds and the length of the animal studies exceed the recommended duration of clinical treatment. The amount of Ciprodex® that reaches the middle ear space during clinical use is not likely to be as great as that which was present in the guinea pigs that were the subjects in the toxicity testing.

The guinea pig data show that Ciprodex® Otic Suspension administered twice daily for 7 days appears to be a reasonably safe treatment for acute otitis media with otorrhea in patients ≥6 months of age with tympanostomy tubes or acute otitis externa in patients ≥6 months of age.

General Toxicology Issues: None.

Recommendations: The pharmacologist has no objection to the approval of NDA 21,537 for Ciprodex® Otic Suspension.

Labeling with basis for findings:

The Ciprodex® label should be consistent with the labels for Cipro® HC and Floxin® Otic. The fourth paragraph ("No signs of local irritation were found...") in the *Precautions/General* section should be deleted unless the sponsor submits data to support it. The pharmacologist found no ophthalmic data from rabbits in this NDA to support the statement. In the *Carcinogenesis, Mutagenesis, Impairment of Fertility* section, the second sentence in the sixth paragraph should be revised to read: "This would be over 100 times the maximum recommended clinical dose of ototopical ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with CIPRODEX® Otic twice per day according to label directions." The last sentence in the last paragraph in this section should be revised to read "The relevance of this study for topical otic use is unknown."

In the section *Pregnancy/Teratogenic Effects*, the first sentence should be modified to read "...oral doses up to 100 mg/kg and IV doses up to 30 mg/kg and have revealed..." In the same section, second paragraph, the last 2 sentences should be deleted, leaving only the categorical language for corticosteroids. Finally, in the *Pediatric Use* section, the should be

deleted. Ocular exposure to ciprofloxacin may not be relevant to otic exposure and there is an implication that the joints were studied following otic administration when they were not. Arthropathy is not really a concern for a product that is given via the otic route since systemic exposure is very low with otic dosing.

X. APPENDIX/ATTACHMENTS:

Addendum to review: None.

Other relevant materials (Studies not reviewed, appended consults, etc.): Nothing to report.

Any compliance issues: None for pharm/tox.

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

/s/

Amy Ellis
6/18/03 10:15:51 AM
PHARMACOLOGIST
The pharmacologist has no objection to the approval of this NDA.
Bob- You signed the paper copy of this review on 6/18/03.

Robert Osterberg
6/18/03 10:40:16 AM
PHARMACOLOGIST

Lillian Gavrilovich
6/18/03 04:31:36 PM
MEDICAL OFFICER

INTEROFFICE MEMORANDUM

DATE: 7/1/03

TO: Daniel Nguyen
Project Manager, HFD-520

FROM: Amy L. Ellis, Ph.D.
Pharmacologist, HFD-520

THROUGH: Robert E. Osterberg, Ph.D.
Pharmacology Team Leader, HFD-520

RE: Review Addendum/Label; NDA 21,537 Ciprodex Otic Suspension

In the original pharm/tox review of this NDA, I recommended deleting a sentence in the *Precautions/General* section ("No signs of local irritation were found when Ciprodex Otic was applied topically in the rabbit eye.") because the sponsor had not submitted any data to support it. After that review was filed, I received a copy of the four month safety update to the NDA which contained study report 099:30:0202, ***A 2-Week Topical Ocular Irritation and Toxicity Study in New Zealand White Rabbits for Evaluation of Ciprofloxacin and Dexamethasone Degradation Products in Ophthalmic Formulations***. This study was conducted to support the use of Ciprodex for ophthalmic indications- the otic and ophthalmic products are the same formula. The sponsor sent in this study report in the four month safety update because they had neglected to include it in the original NDA- they realized after the NDA had been submitted that they had made a statement in the label that they had not supported with data.

No ocular irritation (including microscopic changes) was observed in the rabbit study. The animals were treated unilaterally with drops 4 times daily for 2 weeks. The statement cited above may remain in the label; a similar statement is present in the label for Floxin Otic Solution.

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/s/

Amy Ellis
7/1/03 11:46:26 AM
PHARMACOLOGIST

Robert Osterberg
7/1/03 11:51:11 AM
PHARMACOLOGIST

APPEARS THIS WAY
ON ORIGINAL