CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-799

PHARMACOLOGY REVIEW

NOV 13 1997

Review and Evaluation of Pharmacology and Toxicology Data
Division of Anti-Infective Drug Products, HFD-520

NDA #: 20,799-000

SPONSOR: Daiichi Pharmaceutical Corporation
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AUTHORIZED REPRESENTATIVE: Amy Domanowski, Ph.D.
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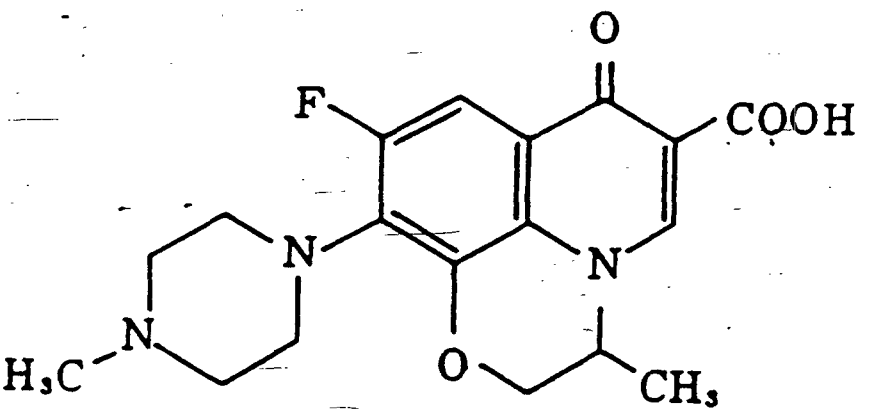
DRUG NAMES: FLOXIN® Otic; ofloxacin otic solution

CATEGORY: Fluoroquinolone antimicrobial

STRUCTURAL FORMULA:



RELATED SUBMISSIONS: INDs

and NDAs

19,735 (FLOXIN® Tablets), 20,087 (FLOXIN® IV), 19,921 (Ocuflox™)

This submission includes letters of authorization to cross reference the NDAs listed above.

NUMBER OF VOLUMES: 11 for Pharm/Tox (385 total)

DATE CDER RECEIVED: 12/18/96

DATE ASSIGNED: 12/30/96 (by KS); 1/2/97 (by REO)

DATE REVIEW STARTED: 1/2/97

DATE 1ST DRAFT COMPLETED: 9/25/97

DATE REVIEW ACCEPTED BY TEAM LEADER: November 13, 1997

REVIEW OBJECTIVES: To ascertain whether the nonclinical studies submitted by the sponsor adequately demonstrate the potential toxicity of this compound with special regard for the ear and its associated organs and to determine if this drug product meets safety standards allowing it to be approved for marketing.

PROPOSED DOSAGE FORM AND ROUTE OF ADMINISTRATION:

Ofloxacin Otic Solution contains the following ingredients:

Ofloxacin	3 mg/ml
Benzalkonium Chloride	0.025 mg/ml
Sodium Chloride	9 mg/ml
Hydrochloric Acid	as needed for adjustment of pH to 6.5 ± 0.5
Sodium Chloride	as needed for adjustment of pH to 6.5 ± 0.5
Water for Injection	q.s.

PROPOSED CLINICAL INDICATIONS AND DOSAGE REGIMENS:

Otitis Externa:

Children (1-12 years old)	5 drops (0.25 ml, 0.75 mg ofloxacin) into affected ear/s, twice daily for 10 days
Adults and Children over 12 years old	10 drops (0.5 ml, 1.5 mg ofloxacin) into affected ear/s, twice daily for 10 days

Acute Otitis Media in Children with Tympanostomy Tubes:

Children (1-12 years old)	5 drops (0.25 ml, 0.75 mg ofloxacin) into affected ear/s, twice daily for 10 days- pump tragus to facilitate penetration of drops into middle ear

Chronic Suppurative Otitis Media with Perforated Tympanic Membranes:

Adults and Children over 12 years old	10 drops (0.5 ml, 1.5 mg ofloxacin) into affected ear/s, twice daily for 14 days

INDEX OF NONCLINICAL STUDIES SUBMITTED TO THIS NDA
(and location of review):

Pharmacokinetic Studies:

Experimental Study on the Distribution of OFLX into the Brain After Topical Administration to the Middle Ear Cavity (8280J-MET001)
IND

The Determination of OFLX in Guinea Pig Serum Using High Performance Liquid Chromatography with Fluorescence Detection Specific to Daiichi Pharmaceutical (8280A-MET102)
reviewed below

Analysis of Trans-Tympanic Membrane Permeability of OFLX Otic Solution (8280A-MET003)
IND

Toxicology Studies:

Safety Evaluation of OFLX in Rabbits I. Ocular Irritation Test and Systemic Influences with Topical Application for One Week (8280J-TOX001)
IND

Safety Evaluation of OFLX in Rabbits II. Ocular Irritation Test and Systemic Influences with Topical Application for Four Weeks (8280J-TOX002)
IND

Six Month Chronic Eye and Systemic Toxicity Study of OFLX Solution in Rabbits (8280A-TOX015)
NDA 19,921

Six Month Ocular Toxicity Study in Cynomolgus Monkeys- Included via cross reference
NDA 19,921

Ocular Irritation Study of OFLX Eye Drops in Rabbits (8280J-TOX003)
IND

One-Month Subacute Ocular and Systemic Toxicity Study of Degraded (by Exposure to Photo-irradiation) Ofloxacin in Rabbits- Included via cross reference
NDA 19,921

Experimental Study of the Influence of OFLX Otic Solution Upon the Inner Ear (8280J-TOX005)
IND

INDEX OF NONCLINICAL STUDIES SUBMITTED TO THIS NDA
(and location of review):

Pharmacokinetic Studies:

Experimental Study on the Distribution of OFLX into the Brain After Topical Administration to the Middle Ear Cavity (8280J-MET001)
IND

The Determination of OFLX in Guinea Pig Serum Using High Performance Liquid Chromatography with Fluorescence Detection Specific to Daiichi Pharmaceutical (8280A-MET102)
reviewed below

Analysis of Trans-Tympanic Membrane Permeability of OFLX Otic Solution (8280A-MET003)
IND

Toxicology Studies:

Safety Evaluation of OFLX in Rabbits I. Ocular Irritation Test and Systemic Influences with Topical Application for One Week (8280J-TOX001)
IND 45,448-000

Safety Evaluation of OFLX in Rabbits II. Ocular Irritation Test and Systemic Influences with Topical Application for Four Weeks (8280J-TOX002)
IND

Six Month Chronic Eye and Systemic Toxicity Study of OFLX Solution in Rabbits (8280A-TOX015)
NDA 19,921

Six Month Ocular Toxicity Study in Cynomolgus Monkeys- Included via cross reference
NDA 19,921

Ocular Irritation Study of OFLX Eye Drops in Rabbits (8280J-TOX003)
IND

One-Month Subacute Ocular and Systemic Toxicity Study of Degraded (by Exposure to Photo-irradiation) Ofloxacin in Rabbits- Included via cross reference
NDA 19,921

Experimental Study of the Influence of OFLX Otic Solution Upon the Inner Ear (8280J-TOX005)
IND

A Study of the Influence of OFLX on the Cochlea After Topical Administration Into the Middle Ear (8280J-TOX006)
IND

Ototoxicity of Topical Otomicrobial Agents (8280A-TOX010)
IND

Effect of OFLX Otic Solution on the Middle Ear and Cochlea of Juvenile Guinea Pigs (8280J-TOX009)
IND

Toxicology Study of OFLX Administered by Ear to Guinea Pigs for 28 Days. Part I (8280E-TOX013.1)
IND

Toxicology Study of OFLX Administered by Ear to Guinea Pigs for 28 Days. Part II (8280E-TOX013.2)
IND

One Month Ototoxicity Study of a 1.0% Otic Solution of OFLX in the Guinea Pig (8280A-TOX012.1)
IND

A Microscopic Evaluation of the Ossicles from Guinea Pigs Treated with Ofloxacin (8280A-TOX012.2)
reviewed below

Ototoxicity of DL-8280 in Guinea Pigs (8280J-TOX007)
IND

Chronic Toxicity Study of Orally Administered DL-8280 to Rats for 26 Weeks (8280J-TOX016; DS-1567
NDA 19,921

One Year Oral Toxicity Study in Cynomolgus Monkey (8280J-TOX017; DS-1638)
NDA 19,921

Maximization Test on OFLX in Guinea Pigs (8280J-TOX004)
IND

REVIEWS OF NONCLINICAL STUDIES:

Pharmacokinetic Study:

The Determination of OFLX in Guinea Pig Serum Using High Performance Liquid Chromatography with Fluorescence Detection Specific to Daiichi Pharmaceutical (8280A-MET102; Analytical Project No. 951050/DXF)

Report dated 11/16/95; Amendment dated 4/1/96

Vol. 1.13, p. 189 - Vol. 1.14, p. 175

Method: Guinea pig serum samples were diluted with 50 mM potassium dihydrogen orthophosphate and applied to columns. D51-4819 was used as an internal standard to determine the efficiency of the extraction for each sample. The columns were washed with mM potassium dihydrogen orthophosphate, then ofloxacin and D51-4819 were eluted using % tetrahydrofuran in mM potassium dihydrogen orthophosphate. The eluent was evaporated to dryness, and the residue was reconstituted with % tetrahydrofuran in water and injected onto the system. A analytical column microns, cm mm) with a mobile phase of 94.5 : 4.5 : 1 aqueous mM potassium dihydrogen orthophosphate buffer (pH 2.0 with phosphoric acid): tertahydrofuran: ammonium acetate was used for The retention times of ofloxacin and D51-4819 were 7 and 12 minutes, respectively, and they were measured using a fluorescence detector with an excitation wavelength of nm and an emission wavelength of nm. None of the extracted components of guinea pig serum interfered with the detection of ofloxacin or the internal standard. The lower limit of detection of this method was ng/ml and the upper limit was ng/ml.

Results: This assay for measuring the level of ofloxacin in guinea pig serum appears to have been acceptably validated and used appropriately. Ofloxacin in guinea pig serum was stable for at least 172 days when stored at -22°C. The samples from the Schaefer study (TOX-012.1) that were sent to were analyzed within this period of time. The data on the amounts of ofloxacin in guinea pig serum after intratympanic dosing are included in the review of the Schaefer study (see IND

Toxicology Study:

A Microscopic Evaluation of the Ossicles from Guinea Pigs Treated with Ofloxacin (8280A-TOX012.2)

Report dated 10/30/96, U.S. GLP

Vol. 2, pp. 001- 046

Animals, Diet, Drug Dose, Route of Administration and Length of Study: Same as for TOX012.1, which can be found in IND The male and female Strain II (2/NCr; National Cancer Institute) guinea pigs used in this ossicle evaluation were satellite groups from that study. Dosing solutions were administered via a surgically implanted sterile catheter that was inserted into the left middle ear through a hole in the tympanic bulla. The guinea pigs received 0.1 ml twice daily for 30 days. Each dose group had 3 animals/sex devoted to ossicle evaluation, but one male and one female from the control group were eliminated from the study due to displacement of their dosing catheters. After the animals were sacrificed, the temporal bones were harvested, stored in % paraformaldehyde, and shipped on ice from (where the in-life portion of the study was conducted) to the The bullae were dissected free of the bone and opened to allow for observation of and access to the middle ear. They were decalcified over a period of weeks using EDTA in a phosphate buffer with % glutaraldehyde. Next, the bullae were dehydrated using ethanol at gradually increasing concentrations. After a concentration of % ethanol was reached, it was replaced with The dehydrated tissues were embedded in resin, cured, and cut into micron sections. Sections containing the ossicles (at least 3 per animal) were stained with Richards' stain and examined microscopically.

The treatment groups were as follows:
1. 0.9% saline/0.0025% benzalkonium chloride
2. 0.3% Ofloxacin/0.0025% benzalkonium chloride, clinical formulation
3. 1.0% Ofloxacin/0.0025% benzalkonium chloride
4. 10% Neomycin

Results: Mild tissue reactions were observed in the middle ears of guinea pigs treated with the vehicle or 0.3% ofloxacin. In these animals, the periosteum lining the middle ear cavity was slightly thickened and occasional mild vesiculation was observed. The investigators believed that these effects may have been due to irritation from the application of fluids to the middle ear because there was only a minimal difference between animals from the vehicle control group and those from the 0.3% ofloxacin groups. Although the report said that the reaction was somewhat more noticeable in the latter group, the pathologist considered the overall middle ear changes in both treatment groups to be minimal.

Tissue reactions of greater severity were observed in the middle ears of guinea pigs treated with 1% ofloxacin or 10% neomycin. Hypertrophy and vesiculation of the periosteum was pronounced in both of these treatment groups and fibrous tissue proliferation involving the tympanic membrane, periosteum, and ossicles were observed in some animals. Changes in the stapedial-vestibular joint suggesting ossification and fixation were observed in several guinea pigs from the 1% ofloxacin group and in one animal from the 10% neomycin group. New tissue surrounding the incal-stapedial joint was observed in many animals from both the 1% ofloxacin and 10% neomycin groups. The incidence and overall severity of middle ear pathology was similar in the 1% ofloxacin and 10% neomycin treatment groups.

Ofloxacin caused minimal irritation to the middle ears of guinea pigs when applied as a 0.3% solution for one month. The tissue reactions observed in 0.3% ofloxacin treated animals were very similar to those seen in animals treated with vehicle. As has been observed in other studies, 1% ofloxacin is irritating to the middle ear of the guinea pig when applied intratympanically for one month. It did not, however, appear to cause fluoroquinolone-specific damage (often described as "blistering") to the cartilage at the ossicular articulations. The ossification and tissue proliferation associated with the ossicular joints appeared to be associated with irritation and were observed in guinea pigs that were treated with either 1% ofloxacin or 10% neomycin. Changes in the ossicles or ossicular articulations were not observed in guinea pigs treated with 0.3% ofloxacin.

SUMMARY AND EVALUATION OF OFLOXACIN OTOTOXICITY:

In guinea pigs, ofloxacin is not readily absorbed across an intact tympanic membrane, but it is rapidly absorbed if administered directly into the middle ear. The drug did not distribute directly to the brain upon administration to the middle ear of guinea pigs, but low levels did reach the brain via the blood stream after absorption. Use of FLOXIN® Otic solution by humans is extremely unlikely to result in significant systemic levels of ofloxacin because a total of only 3 mg/day is administered to each affected ear. Children under 12 year of age would receive only 1.5 mg/day in each affected ear.

Ofloxacin was not a sensitizer in the guinea pig maximization assay and it did not cause ocular irritation in rabbits when a 0.3% solution (pH 6.0-6.6) was applied 8 times per day for 1 week. Ocular irritation was not observed in rabbits treated with up to 0.5% ofloxacin (pH 6.5) 4 times per day for 1 month.

Orally administered ofloxacin did not appear ototoxic to guinea pigs (no loss of pinna reflex in response to tones of 1-20 kHz and no inner ear pathology or loss of cochlear hair cells) when given for approximately one month at doses up to 200 mg/kg/day. Several guinea pig studies demonstrated that 0.3% ofloxacin was not ototoxic when applied directly into the middle ears of these animals for up to one month. This concentration of ofloxacin was not more irritating to the middle ear than the saline/benzalkonium chloride vehicle and it was not associated with significant loss of hearing as measured by Auditory Brainstem Response. Additionally, 0.3% did not induce significant loss of cochlear hair cells. Guineas pig are a very sensitive model for demonstrating the ototoxic potential of drugs; thus, the guinea pig data submitted by the sponsor provide reassurance that 0.3% ofloxacin is likely to be safe for otic use by humans. Cortisporin® was toxic to the cochlear hair cells of guinea pigs when administered into the middle ear for 7 days, and it is frequently used for otitis in humans (even in cases where the tympanic membrane is not intact). There is a greater margin of safety for FLOXIN® Otic Solution compared to Cortisporin® Otic products as demonstrated in this guinea pig study. Although results from a guinea pig study where 1% ofloxacin was administered to the middle ear for 7 days did not show cochlear hair cell loss, 1/10 guinea pigs treated with the same concentration of this drug for one month had significant hair cell loss at the base of the cochlea with more moderate apical hair cell loss, a pattern consistent with that produced by ototoxic agents. This animal also had moderate hearing loss as measured by ABR. No evidence of ototoxicity was observed in the rest of the animals in this treatment group. It is possible that administration of 1% ofloxacin for 30 days may be approaching an

ototoxic level for guinea pigs. Data indicate that 1% ofloxacin is irritating to the middle ear of guinea pigs and was associated with hypertrophy and vesiculation of the periosteum lining the middle ear cavity, and fibrous tissue proliferation involving the tympanic membrane, periosteum, and ossicles. The ossification and tissue proliferation associated with the ossicular joints appeared to be associated with irritation and did not appear to be ofloxacin-specific, as it was also observed in guinea pigs treated with 10% neomycin.

Based upon the guinea pig data, 0.3% ofloxacin otic solution should be reasonably safe for 10-14 days of therapy for the clinical indications requested by the sponsor.

LABELING:

Please note that suggested additions are underlined and some of the suggested deletions are struck out. The pharmacologist is not recommending that any specific portion of the text be underlined in the printed label.

RECOMMENDATION: The pharmacologist has no objection to the approval of this NDA for 0.3% ofloxacin otic solution. Suggested revisions to the sponsor's proposed label can be found above.

/S/

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

Orig. NDA
cc:
HFD-520
HFD-520/Pharm Team Ldr/Osterberg
HFD-520/Pharm/Ellis
HFD-520/MO/McDonald
HFD-520/Chem/Shetty
HFD-520/CSO/Duvall-Miller
HFD-520/Micro/King

Concurrence Only:
HFD-520/REOsterberg RDO 11/13/97
HFD-520/LGavrilovich LG 11/14/97

Appendices:
IND
IND
IND