# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

## 20-799

# MICROBIOLOGY REVIEW

APR 23 1997

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF SUPPLEMENT
22 April 1997

A. 1. NDA 20-799
APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, NJ 07024

2. PRODUCT NAME: FLOXIN® Otic (Ofloxacin Otic Solution) 0.3%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile otic preparation for instillation into the ear.

4. METHODS OF STERILIZATION:
The product is filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of otitis externa in adults and children, chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane, and acute otitis media in children with tympanostomy tubes.

B. 1. DATE OF INITIAL SUBMISSION: 18 December 1996

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS:

| Document | Subject | Document Holder |
|---|---|---|
| IND | | |
| IND | | |
| IND | | |
| IND | | |
| NDA 19-735 | Ofloxacin Tablets | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 20-087 | Ofloxacin Injection | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 19-921 | Ofloxacin Ophthalmic Solution | Allergan, Inc. |
| DMF | | |

4. ASSIGNED FOR REVIEW: 5 February 1997

C. REMARKS: The drug product is manufactured, packaged, and labeled by:

Parke-Davis Sterile Products
Division of Warner-Lambert
870 Parkdale Road

Rochester, Michigan 48307

Establishment Registration #: 18-18977

D. CONCLUSIONS: The application is approvable pending resolution of microbiology issues.

/S/

22 Apr 1997

Paul Stinavage, Ph.D.

FTC 4/23/97

cc: Original NDA 20-799
HFD-520/B.V. Shetty/B.D. Miller
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 22 April 1997
R/D initialed by P. Cooney

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2
17 October 1997

A. 1. NDA 20-799

APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, NJ 07024

2. PRODUCT NAME: FLOXIN® Otic (Ofloxacin Otic Solution) 0.3%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile otic preparation for instillation into the ear.

4. METHODS OF STERILIZATION:
The product is filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of otitis externa in adults and children, chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane, and acute otitis media in children with tympanostomy tubes.

B. 1. DATE OF INITIAL SUBMISSION: 18 December 1996

2. DATE OF AMENDMENT: 31 July 1997

3. RELATED DOCUMENTS:

| Document | Subject | Document Holder |
|---|---|---|
| IND | | |
| IND | | |
| IND | | |
| IND | | |
| NDA 19-735 | Ofloxacin Tablets | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 20-087 | Ofloxacin Injection | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 19-921 | Ofloxacin Ophthalmic Solution | Allergan, Inc. |
| DMF | | |

4. ASSIGNED FOR REVIEW: 17 October 1997

C. REMARKS: The drug product is manufactured, packaged, and labeled by:

Parke-Davis Sterile Products
Division of Warner-Lambert
870 Parkdale Road
Rochester, Michigan 48307

Establishment Registration #: 18-18977

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns.

/S/ 17 October 1997
Paul Stinavage, Ph.D.
RAC 10/17/97

cc: Original NDA 20-799
HFD-520/B.V. Shetty/B.Duvall-Miller
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 17 October 1997
R/D initialed by P. Cooney

NDA 20-799/Duval-Hill

NOV 26 1997

REVIEW FOR HFD-520
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3
26 November 1997

A. 1. NDA 20-799
APPLICANT: Daiichi Pharmaceutical Corporation
One Parker Plaza
Fort Lee, NJ 07024

2. PRODUCT NAME: FLOXIN® Otic (Ofloxacin Otic Solution) 0.3%

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile otic preparation for instillation into the ear.

4. METHODS OF STERILIZATION:
The product is filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The product is used for treatment of otitis externa in adults and children, chronic suppurative otitis media in adolescents and adults with perforated tympanic membrane, and acute otitis media in children with tympanostomy tubes.

B. 1. DATE OF INITIAL SUBMISSION: 18 December 1996

2. DATE OF AMENDMENT: 25 November 1997

3. RELATED DOCUMENTS:

| Document | Subject | Document Holder |
|---|---|---|
| IND | | |
| IND | | |
| IND | | |
| IND | | |
| NDA 19-735 | Ofloxacin Tablets | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 20-087 | Ofloxacin Injection | The R.W. Johnson Pharmaceutical Research Institute |
| NDA 19-921 | Ofloxacin Ophthalmic Solution | Allergan, Inc. |
| DMF | | |

4. ASSIGNED FOR REVIEW: 17 October 1997

C. REMARKS: The drug product is manufactured, packaged, and labeled by:

Parke-Davis Sterile Products
Division of Warner-Lambert
870 Parkdale Road
Rochester, Michigan 48307

Establishment Registration #: 18-18977

D. CONCLUSIONS: The application is recommended for approval on the basis of the data provided.

/S/

26 November 1997

Paul Stinavage, Ph.D.

PHC 11/26/97

cc: Original NDA 20-799
HFD-520/B.V. Shetty/B.Duvall-Miller
HFD-805/Consult File/Stinavage
HFD-520/Division Files

Drafted by: P. Stinavage, 26 November 1997
R/D initialed by P. Cooney

520

Division of Anti-Infective Drug Products (HFD-520)
Clinical Microbiology Review Notes #1

NDA # 20-799 DATE COMPLETED: 10 JUN 97

APPLICANT(NDA):

Daiichi Pharmaceutical Corporation
One Parker Plaza
400 Kelby Street
Fort Lee, NJ 07024

CHEM/THER. TYPE: fluoroquinolone

SUBMISSION REVIEWED: Original NDA submission

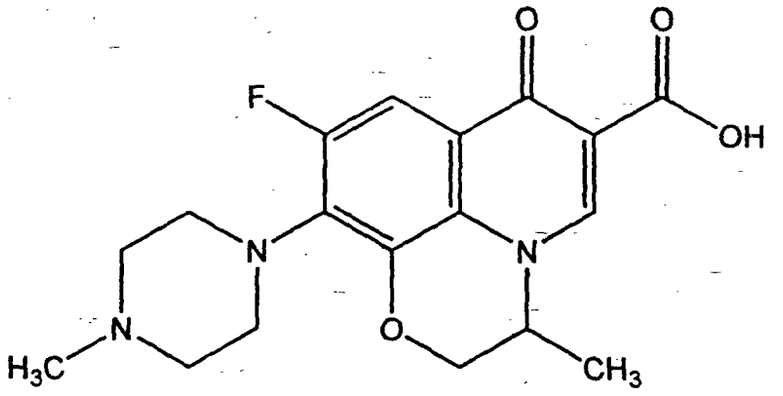
PROVIDING FOR: clinical microbiology studies in support of the proposed labeling for otic ofloxacin.

PRODUCT NAMES(S):
Proprietary: Floxin otic

Non-Proprietary/USAN: otic ofloxacin

CHEMICAL NAME, STRUCTURAL FORMULAS, MOLECULAR FORMULA, MOL. WT.

Ofloxacin, 9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3 de]-1,4-benzoxazine-6-carboxylic acid hemihydrate shown in the figure below, is composed of equal amounts of the D- and L-isomers, and is a synthetic fluorinated carboxyquinolone.




Empirical formula: $C_{18}H_{20}FN_3O_4$
MW 361.38

**DOSAGE FORMS(S)** otic

**STRENGTHS:** 0.3%

**ROUTE(S) OF ADMINISTRATION:** otic

**PHARMACOLOGICAL CATEGORY:** antiinfective

**DISPENSED:** X Rx ___ OTC

**INITIAL SUBMISSION:**
Received by CDER: 18 December, 1996
Received by Reviewer: 6 January, 1997
Review Completed: 10 JUN 97

**AMENDMENT(S)**
Received by CDER: N/A
Received by Reviewer:
Review Completed:

Microbiological Review Notes:

TABLE OF CONTENTS

INTRODUCTION

Ofloxacin is composed of equal amounts of the D- and L-isomers, and it is a synthetic fluorinated carboxyquinolone with antibacterial activity. The antibacterial activity of ofloxacin resides primarily in the L-isomer. Ofloxacin differs from the earliest quinolones (e.g., nalidixic acid) by the presence of a fluorine and an N-methylpiperazine substituent, and is chemically distinct from most other recent quinolones with respect to the presence of a benzoxazine ring.

PRECLINICAL EFFICACY

In vitro

Mechanism(s) of Action.

Quinolones, such as ofloxacin, exert their antibacterial activity by inactivating subunit A (Gyr A) of the deoxyribonucleic acid (DNA) gyrase holoenzyme, a topoisomerase II. To a lesser degree, fluoroquinolones antagonize topoisomerase IV. This enzyme is also involved in the maintenance of the bacterial DNA superhelix.

The position of the methyl substituent on the benzoxazine ring appears to significantly affect the antibacterial activity of ofloxacin. It is this site which affects the steric disposition of ofloxacin as two isomers, the dextrorotatory and levorotatory isomers. The levorotatory isomer has distinctly greater inhibitory activity than does the dextrorotatory isomer against DNA gyrase.

Antimicrobial Spectrum of Activity.

Ofloxacin exerts a high degree of antibacterial activity against aerobic gram-positive bacteria, including staphylococci such as *Staphylococcus aureus* and *Staphylococcus epidermidis*; streptococci such as *Streptococcus pneumoniae* and *Streptococcus pyogenes*; and enterococci such as *Enterococcus faecalis*. Ofloxacin exhibits significant activity against gram-negative bacteria, including non-lactose fermentors such as *Pseudomonas aeruginosa* and lactose fermentors such as members of the enterobacteriaceae.

Also see Epidemiological studies below for exhaustive data to support these claims.

Mechanism(s) of Resistance Studies (Panel).

Moderately and highly ofloxacin-resistant clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA) appear to be altered in the subunit A of DNA gyrase (i.e., mutations mapped to the *gyrA* locus). Ofloxacin-resistant MRSA also contained secondary mutations that affected either ofloxacin uptake or efflux. In addition to alterations in the *gyrA* subunit of DNA gyrase, changes in the Par C

subunit of topoisomerase IV have also been described. Such mutants are significantly more resistant to quinolones than organisms altered at *gyrA* alone. Significant cross-resistance exists for most or all members of fluoroquinolones among bacteria resistant to ofloxacin.

The applicant claims that no enzymes able to inactivate or degrade quinolones have been identified. Thus, as expected, other enzymes which modify beta lactams or aminoglycosides exert no influence over the activity of ofloxacin. Furthermore, plasmid-mediated resistance to quinolones has not been reported among clinical isolates. Thus, spread of resistance to quinolones is significantly limited, and appears to involve the selection of new mutants accompanied by the expansion of resistant clones.

Epidemological Studies (Published Literature).

The following data represent *in vitro* studies involving ofloxacin and other representative quinolones for organisms usually considered potential pathogens in the ear, specifically for otitis externa and otitis media with either tympanostomy tubes or chronic perforation of the tympanic membrane.

The information in these tables consists of the range of all MIC values and the range of the $MIC_{90}$ values from the cited literature. These data include isolates from Japan, Europe, and the United States. Thus, these bacteria are truly representative of a broad cross section of organisms.

**Text Table 2.1:1. MIC Range and $MIC_{90}$ Range of Antibiotic to Otic Pathogens from Literature**

| Pathogen | No. of Isolates | Compound | MIC Range (µg/mL) | $MIC_{90}$ Range (µg/mL) |
|---|---|---|---|---|
| *Enterococcus faecalis* | 1441 | Ofloxacin | 0.39-100 | 2.0-64 |
| | 1431 | Ciprofloxacin | 0.25> 128 | 1.0-32 |
| | 182 | Lomefloxacin | 3.13-128 | 4-128 |
| | 610 | Norfloxacin | 1.56-50 | 3.13-16 |
| *Staphylococcus aureus* | 3285 | Ofloxacin | 0.05->100 | 0.5-25 |
| *Staphylococcus aureus* (unspecified susceptibility to methicillin) | 3026 | Ciprofloxacin | 0.015-32 | 0.25-32 |
| | 346 | Lomefloxacin | 0.125-128 | 1-32 |
| | 812 | Norfloxacin | 0.2-128 | 1->100 |
| *Staphylococcus aureus (MRSA)* | 2359 | Ofloxacin | 0.1-200 | 0.5->100 |
| | 2321 | Ciprofloxacin | 0.05->800 | 0.38->100 |
| | 301 | Lomefloxacin | 0.39->128 | 3.13->64 |
| | 1040 | Norfloxacin | 0.2-200 | 4-128 |
| *Staphylococcus aureus (MSSA)* | 1463 | Ofloxacin | 0.19->100 | 0.25-2 |
| | 1523 | Ciprofloxacin | 0.05->100 | 0.39-3.13 |
| | 212 | Lomefloxacin | 0.39>100 | 1-1.56 |
| | 657 | Norfloxacin | 0.006-128 | 1-4 |
| *Streptococcus pneumoniae* | 762 | Ofloxacin | 0.39-25 | 2-6.25 |
| | 857 | Ciprofloxacin | 0.03-64 | 0.78-6.25 |
| | 212 | Lomefloxacin | 1.56-25 | 8-25 |
| | 136 | Norfloxacin | 0.5-25 | 8-16 |
| *Citrobacter freundii* | 525 | Ofloxacin | ≤0.05->100 | 0.5->100 |
| | 506 | Ciprofloxacin | ≤0.004->100 | 0.03->100 |
| | 72 | Lomefloxacin | ≤0.06-0.25 | 0.25-6.25 |
| | 101 | Norfloxacin | 0.03->100 | 0.5-6.25 |

(Continued)

## Text Table 2.1:1. MIC Range and $MIC_{90}$ Range of Antibiotic to Otic Pathogens from Literature

| Pathogen | No. of Isolates | Compound | MIC Range (µg/mL) | $MIC_{90}$ Range (µg/mL) |
|---|---|---|---|---|
| *Enterobacter cloacae* | 1413 | Ofloxacin | ≤0.03-100 | 0.12-25 |
| | 1435 | Ciprofloxacin | ≤0.006-100 | 0.03-12.5 |
| | 184 | Lomefloxacin | ≤0.03-32 | 0.25-12.5 |
| | 628 | Norfloxacin | ≤0.03-32 | 0.2-32 |
| *Escherichia coli* | 5417 | Ofloxacin | 0.003-64 | ≤0.06-2 |
| | 5257 | Ciprofloxacin | 0.003-32 | 0.013-0.78 |
| | 237 | Lomefloxacin | ≤0.03-1 | ≤0.06-0.39 |
| | 925 | Norfloxacin | 0.015-2 | 0.1-3.13 |
| *Haemophilus influenzae* | 743 | Ofloxacin | 0.013-6.25 | 0.025-0.1 |
| | 797 | Ciprofloxacin | 0.003-1.56 | ≤0.006-0.1 |
| | 147 | Enoxacin | 0.12-0.5 | 0.05-0.39 |
| | 96 | Lomefloxacin | ≤0.063-0.5 | 0.05-0.1 |
| *Klebsiella oxytoca* | 332 | Ofloxacin | ≤0.03-16 | 0.1-0.2 |
| | 332 | Ciprofloxacin | ≤0.006-8 | 0.012-0.20 |
| | 66 | Lomefloxacin | ≤0.06-0.39 | ≤0.06-1.56 |
| *Klebsiella pneumoniae* | 2267 | Ofloxacin | 0.012-25 | 0.19-3.13 |
| | 2250 | Ciprofloxacin | ≤0.006-8 | ≤0.05-0.78 |
| | 251 | Lomefloxacin | 0.012-64 | 0.12-4 |
| | 697 | Norfloxacin | ≤0.03-64 | 0.2-3.13 |
| *Moraxella (Branhamella) catarrhalis* | 207 | Ofloxacin | ≤0.03-0.78 | 0.1-0.2 |
| | 280 | Ciprofloxacin | ≤0.013-0.2 | 0.03-0.2 |
| | 30 | Lomefloxacin | ≤0.063-0.25 | NR |
| | 88 | Norfloxacin | 0.12-1.56 | 0.25-0.39 |
| *Proteus mirabilis* | 1047 | Ofloxacin | 0.025-50 | 0.12-0.5 |
| | 918 | Ciprofloxacin | ≤0.008-1 | 0.025-0.12 |
| | 200 | Lomefloxacin | ≤0.03-8 | 0.25-0.5 |
| | 415 | Norfloxacin | 0.025-2 | 0.1-1 |
| *Pseudomonas aeruginosa* | 3367 | Ofloxacin | ≤0.03-128 | 2-100 |
| | 3230 | Ciprofloxacin | 0.008-64 | 0.39-25 |
| | 243 | Lomefloxacin | 0.25-128 | 4-12.5 |
| | 715 | Norfloxacin | 0.1-100 | 4-50 |

Generally, ofloxacin is active against organisms which could be expected as potential otic pathogens. Ofloxacin was comparably active *in vitro* against most potential otic pathogens when compared to other quinolones. These contentions were further supported by an independent FDA literature search for resistance and resistance mechanisms among all isolates from any source in the years from 1988 to 1996. The FDA search is shown below and does not change the original conclusions drawn from the applicant's listings. Overall, ofloxacin possesses an appropriate spectrum of activity for otic infections whether involving otitis externa, chronic suppurative otitis media in adolescents or adults with perforated tympanic membranes or acute otitis media in children with tympanostomy tubes.

| No. | Records | Request |
|---|---|---|
| 1 | 1345 | OFLOXACIN |
| 2 | 56313 | RESISTANCE |
| * 3 | 4 | OFLOXACIN RESISTANCE |

Record 1 of 4 - MEDLINE EXPRESS (R) 1991-1995
TI: North American (United States and Canada) comparative susceptibility of two fluoroquinolones: ofloxacin and ciprofloxacin. A 53-medical-center sample of spectra of activity. North American Ofloxacin Study Group.
AU: Jones-RN; Hoban-DJ
SO: Diagn-Microbiol-Infect-Dis. 1994 Jan; 18(1): 49-56
ISSN: 0732-8893
LA: ENGLISH
AB: Ofloxacin, a newer broad-spectrum fluoroquinolone, was evaluated against > 12,000 clinical isolates in a multicenter surveillance trial in the United States and Canada using the standardized disk diffusion method. A total of 53 geographically diverse clinical microbiology laboratories contributed zone diameter results for ofloxacin, ciprofloxacin, and norfloxacin for urinary tract infection (UTI) isolates; and ofloxacin and ciprofloxacin for respiratory tract infection (RTI) isolates, skin and soft tissue infection (SSTI) isolates, and genital tract pathogen isolates. In both the USA and Canada, ofloxacin was shown to have the wide spectrum of activity as follows: RTI isolates, ofloxacin (92.2%-93.8% susceptible) > ciprofloxacin (89.5%-90.4%); SSTI isolates, ofloxacin (87.1%-93.6%) > ciprofloxacin (78.8%-90.4%); UTI isolates, ofloxacin (91.6%-92.5%) > norfloxacin (87.3%-91.7%) > ciprofloxacin (86.4%-89.7%); and genital tract isolates, ofloxacin (94.0%) > ciprofloxacin (85.4%) (Canada only). US strains resistant to ofloxacin were confirmed by reference laboratory tests. Confirmed ofloxacin resistance, other than among staphylococci or nonenteric bacilli, was rare. The species most often found to be resistant to both ofloxacin and ciprofloxacin were methicillin-resistant staphylococci, Acinetobacter spp., and Enterococcus spp. From these contributing US and Canadian laboratory studies, ofloxacin appears to have a balanced spectrum of potential clinical use (91.8% susceptible aerobic isolates), particularly against Gram-positive pathogens and some species resistant to ciprofloxacin. The combined overall isolate (12,241 isolates) rates of susceptibility for ciprofloxacin (four infection sites) and norfloxacin (UTI only) were 87.3% and 88.8%, respectively. Monitoring for increasing fluoroquinolone resistance should be considered, however, as greater use of drugs in this class develops.
AN: 94298323

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Record 2 of 4 - MEDLINE EXPRESS (R) 1991-1995
TI: Sequential acquisition of norfloxacin and ofloxacin resistance by methicillin-resistant and -susceptible Staphylococcus aureus.
AU: Hori-S; Ohshita-Y; Utsui-Y; Hiramatsu-K
SO: Antimicrob-Agents-Chemother. 1993 Nov; 37(11): 2278-84
ISSN: 0066-4804
LA: ENGLISH
AB: The acquisition of ofloxacin resistance by a susceptible clinical Staphylococcus aureus strain was found to be achieved in two sequential steps: the first step was accompanied by 4-fold increases in the

ofloxacin MIC and 8- to 16-fold increases in the norfloxacin MIC. The second step was accompanied by further increases in both the ofloxacin and the norfloxacin MICs. A mutation of the gyrA gene resulting in an amino acid substitution was found in the second-step but not in the first-step resistant subclone. On the other hand, there was no difference in the accumulation of norfloxacin in the parent strain and the resistant subclones of each step. The rates of mutation to resistance in the steps were (1.58 to 6.81) x 10(-9) and (0.71 to 2.59) x 10(-9), respectively, and did not depend on whether the parent strain was resistant to methicillin. Some implications of these observations for clinical as well as mechanistic aspects of the prevalence of methicillin- and ofloxacin-resistant S. aureus are discussed.
AN: 94113625

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Record 3 of 4 - MEDLINE EXPRESS (R) 1991-1995
TI: The North American component (the United States and Canada) of an International Comparative MIC trial monitoring ofloxacin resistance.
AU: Hoban-DJ; Jones-RN; Harrell-LJ; Knudson-M; Sewell-D
SO: Diagn-Microbiol-Infect-Dis. 1993 Aug-Sep; 17(2): 157-61
ISSN: 0732-8893
LA: ENGLISH
AB: Common lots of reference MIC (minimum inhibitory concentration) method reagents were used to monitor ofloxacin, a newer fluoroquinolone, and 13 other drugs against 3200 recent clinical isolates in February-April 1992. Five medical centers in the United States and Canada contributed 640 strains per facility as follows: Escherichia coli, Staphylococcus aureus, coagulase-negative staphylococci, Klebsiella spp., and Pseudomonas aeruginosa (100 strains each); Streptococcus pneumoniae (40 strains); and Enterobacter cloacae, Serratia marcescens, Salmonella spp., Haemophilus influenzae, and Moraxella catarrhalis (20 strains each). Quality-control strains were processed concurrently, MICs recorded, and data processed at a common location. Selected ofloxacin-resistant isolates were retested at a reference laboratory to confirm resistances and determine cross-resistant patterns. Results indicate the following (a) fluoroquinolones were superior in usable spectrum of activity to other orally administered drugs (for example, cefaclor, cefixime, ampicillin, amoxicillin-clavulanate, minocycline, oxacillin, and trimethoprim-sulfamethoxazole); (b) ofloxacin and ciprofloxacin were generally equal to gentamicin and cefotaxime against commonly isolated Gram-negative pathogens; (c) fluoroquinolone resistance was rare among enteric bacilli, pneumococci (ciprofloxacin > ofloxacin), H. influenzae, and M. catarrhalis, but more common among oxacillin-resistant staphylococci and P. aeruginosa; (d) cross resistance was generally observed between ofloxacin and ciprofloxacin but was species or genus dependent; and (e) a new fluoroquinolone, levofloxacin, demonstrated promising activity against contemporary pathogens.
AN: 94062311

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Record 4 of 4 - MEDLINE EXPRESS (R) 1991-1995
TI: [Therapeutic effect of ofloxacin on intractable pulmonary tuberculosis and ofloxacin resistance of tubercle bacilli isolated from

the patients. Chest DIsease Cooperative Study Unit of National Sanatoriums in Kinki District]
AU: Nakae-I; Nakatani-K; Inoue-S; Takahasi-K; Ikeda-N; Matsumoto-T; Ozawa-S; Sakatani-M; Kita-N; Tanaka-S
SO: Kekkaku. 1991 Apr; 66(4): 299-307
ISSN: 0022-9776
LA: JAPANESE; NON-ENGLISH
AB: Ofloxacin, a synthetic antibacterial pyridone-carboxylic acid derivative, was used in the treatment of intractable pulmonary tuberculosis. In this study, the therapeutic effect of Ofloxacin on pulmonary tuberculosis and Ofloxacin resistance were analyzed. All patients had been hospitalized in eight national sanatoria in Kinki district, and were excreting tubercle bacilli resistant to various anti-tuberculosis drugs agents. Ofloxacin was given to 118 patients orally at a daily dose of 300 mg to 600 mg for more than 3 months. A few anti-tuberculosis drugs, which had failed in the negative conversion of bacilli previously, were used in combination. By Ofloxacin, 23 patients (19.5%) showed negative conversion of tubercle bacilli in sputum culture within 5 months, and they remained culture-negative for at least 6 months after conversion. Side-effects were observed in 2 patients. One complained of arthralgia and the other felt abdominal fullness. But both were not serious. From these results, it was concluded that Ofloxacin was effective for intractable pulmonary tuberculosis. The resistance of tubercle bacilli to Ofloxacin increased significantly after it was used.
AN: 91269621

In vivo

Pharmacokinetics/Bioavailability (Human and animal).

Ofloxacin otic solution is intended solely for the topical treatment of localized infections of the external auditory canal and of the middle ear, where there is direct communication (perforation or tympanostomy tube) between the external auditory canal and middle ear. The local concentrations in the ear canal and middle ear, rather than the systemic levels, will therefore likely determine the microbiological efficacy of this ofloxacin otic solution. The sponsor provided summary data which may be pertinent to microbiological concerns; a description of the summary data is noted below in the context of the proposed infections to be included in the Indications Section of the package insert. The infections include otitis externa, chronic suppurative otitis media in adolescents and adults with perforated tympanic membranes or acute otitis media in children with tympanostomy tubes.

When a 0.1% ofloxacin otic solution was studied with regard to the residual antibacterial activity 30 minutes after application, concentrations ranged from μg/ml in the otorrhea fluid. Concentrations in the mucous membrane, taken from the tympanic cavity, were also studied. Subjects received either 0.3% or 0.5% ofloxacin otic

solution. Mucous membrane was excised, washed with physiological saline, and frozen prior to assay. The subject that received the 0.3% ofloxacin otic solution achieved a level of 19.5 μg/g 90 minutes post-administration. Three subjects received 0.5% ofloxacin otic solution, and achieved the following tissue levels: 49.1 μg/g at 30 minutes post-treatment, 319.5 μg/g at 60 minutes post-treatment, and 35.5 μg/g at 75 minutes post-treatment. These concentrations are generally above the MICs for the majority of potential otic pathogens.

## CLINICAL EFFICACY

### Clinical Microbiology

#### Isolates/relevance to approved indications.

The microbiological data from all the clinical studies was included in the official CANDA submission. The data demonstrate the range of microorganisms expected from ear infections. This range certainly encompasses those microorganisms within the proposed Indications. These microorganisms were tested for susceptibility to ofloxacin. Unfortunately, susceptibility testing does not provide a rational basis for predicting clinical success or failure of the otic formulation of this drug. Although this drug product may provide high residual levels in the ear fluids and tissues upon topical administration, very little data were available about how frequently the subjects retained the high levels for reasonably extended periods.

#### Cross Resistance/Cross Susceptibility Studies.

In general, bacteria which are resistant to one member of the fluoroquinolone class by virtue of a mutation at *gyrA* are resistant to ofloxacin.

### Bacteriological Efficacy

#### Correlation of Test Results with Outcome Statistics.

See Clinical Efficacy section above. Typical data are included in the Excel worksheet.

NDA 20-799
otic ofloxacin
Daiichi

Package Insert.

REMARK(S):

This NDA submission provides ample evidence that ofloxacin has *in vitro* activity against a host of microbial species. However, the relationshi between ofloxacin *in vitro* activity and established breakpoints for systemic use of ofloxacin has not been clarified because standardized *i vitro* susceptibility testing does not provide predictions of outcomes for otic infections. Undeniably, ofloxacin activity has been demonstrated for an extremely wide spectrum of microorganisms; selected

data are noted above in the respective sections dealing with antimicrobial spectrum studies. Clearly, ofloxacin is active against the pathogens requested for listing in the proposed package insert shown below in the Conclusions/Recommendations section.

CONCLUSIONS and/or RECOMMENDATIONS:

From the microbiological perspective, this NDA is approvable pending negotiation of a package insert. The package insert should have a Microbiology section with the text shown below.

/S/ 9/3/97

James R. King
Microbiologist, HFD-520

SMicro/ASheldon
BD#18 Final init 8/6/97 ASS
9/3/97
10 9/8/97

DepDir/LGavrilovich

cc: Orig. NDA # 20,799
HFD-473
HFD-520/DepDir/LGavrilovich
HFD-635
HFD-520/SMicro/ASheldon
HFD-520
HFD-520/Micro/King
HFD-520/MO/McDonald
HFD-520/Pharm/Adeyemo
HFD-520/Chem/Shetty
HFD-520/CSO/Duvall-Miller

Printed for signatures 9/3/97