CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-634/S-008, S-009

20-635/S-007, S-008

MICROBIOLOGY REVIEW

→ Fritsch

NOV 15 1999

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-634/SEI-008 /SLR-007

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 29-OCT-99
CDER DATE: 01-NOV-99
REVIEW ASSIGN DATE: 08-NOV-99
REVIEW COMPLETE DATE: 15-NOV-99

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Phone Number: (908) 704-4198

SUBMISSION REVIEWED: Revisions to Microbiology and Indications and Usage sections of package insert (addition of penicillin-resistant *Streptococcus pneumoniae* to approved community-acquired pneumonia claim).

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

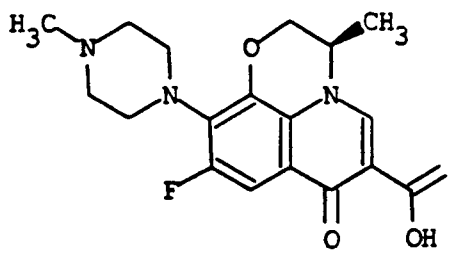
INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI

DOSAGE FORM: Levofloxacin tablets 250 mg and 500 mg/tablet

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Tablets
NONPROPRIETARY/USAN: Levofloxacin tablets
CODE: RWJ-25213-097
CHEMICAL NAME: (-)-(S)-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

STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$ Molecular Weight: 361.38

SUPPORTING DOCUMENTS: NDA 20-635—LEVAQUIN Injection.

BACKGROUND:

The applicant wishes to make revisions to the MICROBIOLOGY subsection and the INDICATIONS AND USAGE section of their package insert. The main revision that they are requesting is the addition of the following wording "(including penicillin-resistant strains)" after *Streptococcus pneumoniae* in their approved community-acquired pneumonia indication and the addition of this wording to list #1 (clinical efficacy shown) in the MICROBIOLOGY subsection.

CONCLUSIONS:

The supplemental application is approvable from the microbiological viewpoint. The only change in the MICROBIOLOGY subsection of the package insert that still needs to be made is revising *Enterobacter agglomerans* to read *Pantoea (Enterobacter) agglomerans*. The rest of this subsection has been revised according to the microbiology review to this supplement (S-008) dated April 23, 1999. The MICROBIOLOGY subsection should read as indicated below.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including penicillin-resistant strains)
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs of this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms
Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcus (Group C/F)
Streptococcus (Group G)
Streptococcus agalactiae
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffi
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes
Pantoea (Enterobacter) agglomerans
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringes

Susceptibility Tests

This section is satisfactory as written. No changes have been made.

Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir _____ Signature _____ Date
HFD-590/TLMicro _____ Signature 11/15/99 Date

CC:
HFD-590/Original NDA # 20634/SEI-008/SLR-007
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ECox
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/JFritsch

J. Fritsch

NOV 15 1999

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-635/SEI-007 /SLR-008	**REVIEWER:**	Peter A. Dionne
	CORRESPONDENCE DATE:	29-OCT-99
	CDER DATE:	01-NOV-99
	REVIEW ASSIGN DATE:	08-NOV-99
	REVIEW COMPLETE DATE:	15-NOV-99

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Phone Number: (908) 704-4198

SUBMISSION REVIEWED: Revisions to Microbiology and Indications and Usage sections of package insert (addition of penicillin-resistant *Streptococcus pneumoniae* to approved community-acquired pneumonia claim).

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

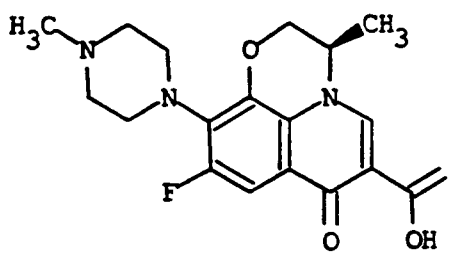
INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI

DOSAGE FORM: Levofloxacin Injection 25 mg/mL, 20 mL vials

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Injection
NONPROPRIETARY/USAN: Levofloxacin injection
CODE: RWJ-25213-097
CHEMICAL NAME: (-)-(S)-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

STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$ Molecular Weight: 361.38

SUPPORTING DOCUMENTS: NDA 20-634—LEVAQUIN Tablets

BACKGROUND:

The applicant wishes to make revisions to the MICROBIOLOGY subsection and the INDICATIONS AND USAGE section of their package insert. The main revision that they are requesting is the addition of the following wording "(including penicillin-resistant strains)" after *Streptococcus pneumoniae* in their approved community-acquired pneumonia indication and the addition of this wording to list #1 (clinical efficacy shown) in the MICROBIOLOGY subsection.

CONCLUSIONS:

The supplemental application is approvable from the microbiological viewpoint. The only change in the MICROBIOLOGY subsection of the package insert that still needs to be made is revising *Enterobacter agglomerans* to read *Pantoea (Enterobacter) agglomerans*. The rest of this subsection has been revised according to the microbiology review to this supplement (S-007) dated April 23, 1999. The MICROBIOLOGY subsection should read as indicated below.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

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Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

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Streptococcus pyogenes

Aerobic gram-negative microorganisms
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Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs of this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

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Chlamydia pneumoniae
Mycoplasma pneumoniae

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Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

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Streptococcus (Group C/F)
Streptococcus (Group G)
Streptococcus agalactiae
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffi
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes
Pantoea (Enterobacter) agglomerans
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringes

Susceptibility Tests

This section is satisfactory as written. No changes have been made.

/S/
Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir___ /S/ Signature_____Date
HFD-590/TLMicro_ Signature 11/15/99 Date

CC:
HFD-590/Original NDA # 20635/SEI-007/SLR-008
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ECox
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/JFritsch

APPEARS THIS WAY
ON ORIGINAL

HFD-590 D. Fritsche

DEC 1 1999

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-634/SEI-008/SLR-007

REVIEWER: Peter A. Dionne
CORRESPONDENCE DATE: 04-NOV-99
CDER DATE: 05-NOV-99
REVIEW ASSIGN DATE: 23-NOV-99
REVIEW COMPLETE DATE: 29-NOV-99

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Phone Number: (908) 704-4198

SUBMISSION REVIEWED: Revised Label. Revisions to Microbiology and Indications and Usage sections of package insert (addition of penicillin-resistant *Streptococcus pneumoniae* to approved community-acquired pneumonia claim).

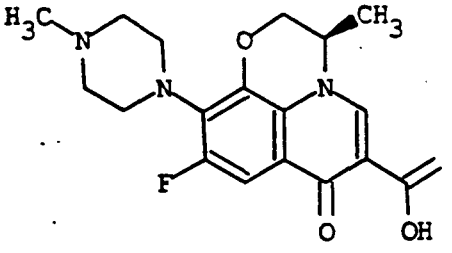
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI

DOSAGE FORM: Levofloxacin tablets 250 mg and 500 mg/tablet

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Tablets
NONPROPRIETARY/USAN: Levofloxacin tablets
CODE: RWJ-25213-097
CHEMICAL NAME: (-)-(S)-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
STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$ Molecular Weight: 361.38

SUPPORTING DOCUMENTS: NDA 20-635—LEVAQUIN Injection.

BACKGROUND:

This submission includes revised labeling. The applicant has added penicillin-resistant strains of *Streptococcus pneumoniae* to their approved community-acquired pneumonia indication and to the microbiology subsection of the label. The microbiology subsection is revised according to the microbiology review dated 6/11/99. The only additional change that should be made is revising *Enterobacter agglomerans* to read *Pantoea (Enterobacter) agglomerans.*

CONCLUSIONS:

From the microbiology viewpoint the labeling will be satisfactory when *Enterobacter agglomerans* is revised to read *Pantoea (Enterobacter) agglomerans.*

RECOMMENDATIONS:

The sponsor should be notified that *Enterobacter agglomerans* should be revised to read *Pantoea (Enterobacter) agglomerans.*

/S/
Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir__ /S/ __Signature 12/3/99 Date
HFD-590/TLMicro__ __Signature 12/1/99 Date

CC:
HFD-590/Original NDA # 20634/SEI-008/SLR-007
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/ECox
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/JFritsch

JUN 10 1999

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-634/SEI-008

REVIEWER:	Peter A. Dionne
CORRESPONDENCE DATE:	31-MAR-99
CDER DATE:	01-APR-99
REVIEW ASSIGN DATE:	06-APR-99
REVIEW COMPLETE DATE:	23-APR-99

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Phone Number: (908) 704-4198

SUBMISSION REVIEWED: Revisions to Microbiology and Indications and Usage sections of package insert (addition of penicillin-resistant and ———————*Streptococcus pneumoniae*.to approved community-acquired pneumonia claim).

DRUG CATEGORY: Antimicrobial: Fluoroquinolone

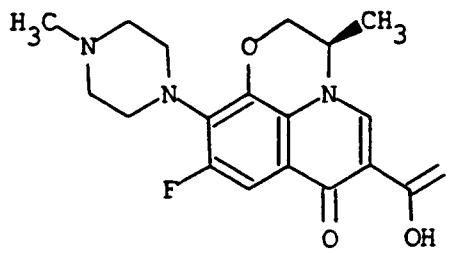
INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI

DOSAGE FORM: Levofloxacin tablets 250 mg and 500 mg/tablet

DRUG PRODUCT NAME

PROPRIETARY:	LEVAQUIN® Tablets
NONPROPRIETARY/USAN:	Levofloxacin tablets
CODE:	RWJ-25213-097
CHEMICAL NAME:	(-)-(S)-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

STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$ Molecular Weight: 361.38

SUPPORTING DOCUMENTS: NDA 20-635—LEVAQUIN Injection.

BACKGROUND:

The applicant wishes to make revisions to the MICROBIOLOGY subsection and the INDICATIONS AND USAGE section of their package insert. The main revision that they are requesting is the addition of the following wording "(including penicillin-resistant/intermediate or [redacted] after *Streptococcus pneumoniae* in their approved community-acquired pneumonia indication and the addition of this wording to list #1 (clinical efficacy shown) in the MICROBIOLOGY subsection.

All of the pre-clinical microbiology information submitted in this supplement has previously been submitted in supplement 006 dated December 17, 1998. This supplement was for the addition of the above wording to list #2 (*in vitro* activity) in the MICROBIOLOGY subsection. The first part of this review is, therefore, identical to the review for supplement 006, which was dated January 12, 1999.

CONCLUSIONS:

The supplemental application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The reviewing Medical Officer will need to decide whether enough evidence has been presented to grant an indication for resistant *Streptococcus pneumoniae*. This will determine whether or not these organisms are listed in the MICROBIOLOGY subsection in list #1 (clinical efficacy) or in list #2 (*in vitro* activity only). The changes needed should be sent to the sponsor. These revisions are listed as recommendations at the end of this review on pages 22-25.

TABLE OF CONTENTS

INTRODUCTION

The applicant has requested the following revisions to the microbiology section of their package insert:

- Add bacterial topoisomerase IV as a target of levofloxacin in the mechanism of action description.
- Add the words "both of which are type II" since topoisomerase IV has been added and there are now two enzymes instead of only DNA gyrase.
- Make minor changes to the wording of the statement that fluoroquinolones differ in chemical structure and mode of action from other antimicrobials. Basically they want to add macrolides to this statement and specify penicillin (
- Add *Streptococcus pneumoniae* (including penicillin-resistant/ strains)

REVISIONS TO MECHANISM OF ACTION AND RESISTANCE STATEMENT

The applicant has submitted one reference (1) to substantiate the addition of topoisomerase IV as a target for the drug. This fact is now well known and topoisomerase IV is in the label of newer fluoroquinolones. It may be added to levofloxacin's label.

The addition of macrolides to the statement about chemical structure and mode of action is also correct and some other fluoroquinolones even mention aminoglycosides. These changes may be made.

ACTIVITY OF LEVOFLOXACIN AGAINST PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

The following data have been submitted to demonstrate that levofloxacin is active against penicillin-intermediate and –resistant strains. Table 1 summarizes the nine studies submitted.

TABLE 1

Summary of *In vitro* Activity of Levofloxacin against *Streptococcus pneumoniae*

Penicillin Susceptibility	No. Isolates	MIC Test Method[a]	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)	Country Year (Ref.)
Pen-S	2699	BMD	≤0.004->8	0.5	1.0	99.9	0.0	0.1	USA
Pen-I	915		≤0.004->8	0.5	1.0	99.6	0.1	0.3	1998
Pen-R	538		0.015-2.0	0.5	1.0	100.0	0.0	0.0	(2)
All	9145	E-test	≤0.002->32	1.0	2.0	97.3	2.1	0.6	USA
Pen-S	6081		0.008->32	1.0	2.0	97.4	2.2	0.4	1997
Pen-I	1817		0.032->32	1.0	2.0	96.9	1.9	1.2	(3)
Pen-R	1247		≤0.002->32	1.0	2.0	97.1	1.8	1.1	
All	690	BMD	0.25->16	NA[b]	1.0	NA	NA	NA	USA
Pen-S	154		0.25-1	0.5	1.0	100	0.0	0.0	1997
Pen-I	150		0.5-16	0.5	1.0	NA	NA	NA	(4)
Pen-R	100		0.5-1	0.5	1.0	100	0.0	0.0	
Pen-S	53	AD	0.25-2.0	1.0	2.0	100	0.0	0.0	USA
Pen-I	84		0.25-2.0	1.0	2.0	100	0.0	0.0	1997
Pen-R	74		0.25-2.0	2.0	2.0	100	0.0	0.0	(5)
All	142	BMD	0.5->8.0	1.0	2.0	NA	NA	NA	USA
Pen-S	123		0.5-2.0	1.0	2.0	100	0.0	0.0	1996
Pen-I-R	19		1.0->8.0	1.0	2.0	NA	NA	NA	(6)
Pen-S	23	AD	0.5-2.0	1.0	1.0	100	0.0	0.0	USA
Pen-R	15		0.5-1.0	1.0	1.0	100	0.0	0.0	1996 (7)
Pen-S	962	BMD	0.12-8.0	0.5	1.0	NA	NA	NA	Canada
Pen-I	91		0.25-8.0	1.0	1.0	NA	NA	NA	1996
Pen-R	36		0.5-8.0	0.5	1.0	NA	NA	NA	(8)
Pen-S	60	AD	NA	0.5	2.0	100	0.0	0.0	South
Pen-I	60		NA	0.5	1.0	100	0.0	0.0	Africa
Pen-R	60		NA	0.5	2.0	100	0.0	0.0	1996 (9)
Pen-S	28	AD	0.39-3.13	0.78	1.56	NA	NA	NA	Japan 1997
Pen-R[c]	21		0.20-1.56	0.78	1.56	NA	NA	NA	(10)

[a] BMD = Broth microdilution; AD = Agar Dilution
[b] NA = data were not available
[c] Pen-S = MIC <0.05 µg/mL; Pen-R = MIC >0.05 µg/mL

These studies demonstrate that levofloxacin MIC_{90} values are unchanged for penicillin-susceptible, -intermediate, and –resistant strains within a study, with the exception of the South African study in which the MIC_{90} for penicillin-intermediate isolates was 1.0 µg/mL compared to MIC_{90} values of 2.0 µg/mL for penicillin-susceptible and –resistant strains. A small increase in the percentage of isolates resistant to levofloxacin was seen in the penicillin-intermediate and penicillin-resistant isolates compared with penicillin-susceptible isolates in one 1997 study conducted in the United States, but this trend was not seen in other studies. Levofloxacin activity remains the same irrespective of the country of origin of the isolates or the *in vitro* susceptibility testing method.

The *in vitro* activity of levofloxacin against *Streptococcus pneumoniae* isolates obtained from subjects treated with levofloxacin during clinical trials that evaluated the efficacy and safety of levofloxacin in the treatment of Community Acquired Pneumonia is summarized in TABLE 2.

TABLE 2
Distribution of Levofloxacin MIC Values (µg/mL) for Levofloxacin-Treated Subjects with Baseline Pathogen *Streptococcus pneumoniae* from Community Acquired Pneumonia Clinical Trials

	No. of Isolates with an MIC (µg/mL)								Levofloxacin	
No. of isolates	<0.25	0.25	0.5	1.0	2.0	4.0	8.0	16	MIC_{50}	MIC_{90}
Pen-S (190)	1	8	27	122	32	0	0	0	1.0	2.0
Pen-I (38)	0	1	10	24	2	0	0	1	1.0	1.0
Pen-R (13)	0	0	3	8	2	0	0	0	1.0	2.0

These data demonstrate that all isolates were susceptible to levofloxacin with the exception of one penicillin-intermediate isolate (penicillin MIC of 1.0 µg/mL) that was levofloxacin-resistant with a levofloxacin MIC of 16 µg/mL. MIC_{50} values remained at 1.0 µg/mL for all isolates regardless of penicillin susceptibility. MIC_{90} values were 2.0 µg/mL for penicillin-susceptible and penicillin-resistant isolates, and 1.0 µg/mL for penicillin-intermediate strains. Since there is a one-dilution error in the method these values are all equivalent.

Barry et al. (11) evaluated the *in vitro* activity of levofloxacin against 654 isolates of *S. pneumoniae*, of which 80 were penicillin-intermediate and 64 were resistant to penicillin. The MIC_{90} for all isolates was 2.0 µg/mL and none was resistant to levofloxacin, while only one strain was levofloxacin-intermediate with a MIC of 4 µg/mL.

In another study (12) of 100 isolates of *S. pneumoniae* (60 penicillin-susceptible, 21 penicillin-intermediate, and 19-penicillin-resistant), none of the isolates was resistant to levofloxacin and the MIC_{90} was 1.0 µg/mL. In comparison, 43% of these isolates were resistant to erythromycin and 11-38% were resistant to expanded spectrum cephalosporins. Erythromycin and cephalosporin susceptibility decreased as penicillin susceptibility decreased.

Plouffe (13) demonstrated that 99.2% of 499 bacteremic isolates of *Streptococcus pneumoniae* collected from Ohio hospitals during 1991-1994 were susceptible to levofloxacin. Of the 39 isolates with penicillin MICs ≥0.12 µg/mL, 38 were susceptible to levofloxacin, as were four of the five penicillin-resistant isolates.

Lister and Edward (14) evaluated the bactericidal activity of levofloxacin against five penicillin-susceptible and five penicillin-resistant strains of *Streptococcus pneumoniae* using an *in vitro* pharmacokinetic model of infection. Levofloxacin was bactericidal against all ten strains with viable counts decreasing 4-6 logs by 6 hours.

George and Morrissey (15) compared the bactericidal activity of levofloxacin with other fluoroquinolones and cefotaxime against penicillin-susceptible, -intermediate, and -resistant strains of *S. pneumoniae*. Levofloxacin was the most bactericidal fluoroquinolone tested and its activity was similar for all strains regardless of susceptibility to penicillin.

Vesga and Craig (16) used murine model of a thigh infection to study the *in vivo* activity of levofloxacin against one penicillin-intermediate and six penicillin-resistant strains of *Streptococcus pneumoniae* in two strains of mice. Levofloxacin was successful against the penicillin-intermediate and -resistant strains. They predicted that based on the 24-hour AUC/MIC required for efficacy and the AUC obtained in patients dosed with 500 mg of levofloxacin once daily, levofloxacin should provide effective therapy for penicillin-resistant *S. pneumoniae*.

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TABLE 7
Summary of *In Vitro* Activity of Penicillin, Macrolides, and Levofloxacin Against *Streptococcus pneumoniae*

Penicillin Status	Macrolide						Levofloxacin						Country Test Method[a]	Reference
	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)		
All	9138	0.125	6.0	80.9	0.9	18.2	9145	1.0	2.0	97.3	2.1	0.6	USA/E-test	3
Pen-S	6094	0.125	0.25	94.9	1.1	4.0	6081	1.0	2.0	97.4	2.2	0.4		
Pen-I	1803	0.125	64	63.5	1.7	34.8	1817	1.0	2.0	96.9	1.9	1.2		
Pen-R	1241	2.0	>256	38.9	1.0	60.1	1247	1.0	2.0	97.1	1.8	1.1		
Pen-S	53	0.03	2.0	NA	NA	NA	53	1.0	2.0	NA	NA	NA	USA/AD	5
Pen-I	84	0.25	4.0	NA	NA	NA	84	1.0	2.0	NA	NA	NA		
Pen-R	74	2.0	>64	NA	NA	NA	74	2.0	2.0	NA	NA	NA		
All	142	0.125	0.25	NA	NA	NA	142	1.0	2.0	NA	NA	NA	USA/BMD	6
Pen-S	123	0.125	0.25	NA	NA	NA	123	1.0	2.0	NA	NA	NA		
Pen-I-R	19	0.125	4.0	NA	NA	NA	19	1.0	2.0	NA	NA	NA		
All[b]	100	≤0.5	>0.5	NA	NA	43.0	100	0.5	1.0	NA	NA	0.0	USA/BMD	12
Pen-S	963	0.12	0.12	98	0.4	1.6	962	0.5	1.0	99.8	0.0	0.2	Canada/BMD	8
Pen-I	91	0.25	0.5	88	2.2	9.8	91	1.0	1.0	97.8	1.1	1.1		
Pen-R	36	0.25	2.0	75	8.3	16.7	36	1.0	1.0	97.2	0.0	2.8		
All (S = 52.7%)	294	NA	>32	37.4	NA	NA	294	NA	1.0	98.3	NA	NA	Japan/BMD	19

[a] BMD = broth microdilution; AD = agar dilution
[b] S = 69, I = 21, R = 19
NA = information not available

DATA FROM CLINICAL STUDIES

This supplement has one new study LOFBIV-PCAP-001 and looks at other Phase 3 community-acquired pneumonia (CAP) studies in which levofloxacin was dosed at 500 mg qd for 7 to 14 days. The sponsor is trying to find enough penicillin-resistant *Streptococcus pneumoniae* isolates to get an indication for CAP caused by penicillin-resistant *S. pneumoniae*. Efficacy data are integrated from all subjects with CAP from whom *S. pneumoniae* was isolated at admission from the following R.W. Johnson Pharmaceutical Research Institute (RWJPRI) studies: LOFBIV-PCAP-001 (recent study), and studies K90-071, M92-075, and LOFBIV-MULT-001 which were included as part of the original NDA.

Due to difficulty encountered in the RWJPRI studies in enrolling subjects with penicillin-resistant *S. pneumoniae*, data from subjects with penicillin-resistant or penicillin-intermediate isolates of *S. pneumoniae* who were enrolled on or before June 12, 1998 in two ongoing non-IND CAP trials, CAPSS-043 and CAPSS-056, also are included in this submission. These studies were sponsored by Ortho-McNeil Pharmaceutical (OMP). In addition, data from one 500 mg qd levofloxacin treated subject with penicillin-resistant *S. pneumoniae* from a Heochst Marion Roussel (HMR) CAP trial FF/93/355/02 were included in this submission. Information regarding [redacted] is presented only for the four RWJPRI sponsored trials since [redacted] *S. pneumoniae* isolates were found in adequate numbers in these studies alone.

Approximately 2400 subjects with CAP were enrolled across the seven studies. Approximately 1800 received levofloxacin 500 mg qd. Efficacy data are presented for 280 levofloxacin treated subjects with *S. pneumoniae* isolates. All but nine isolates came from RWJPRI sponsored studies. In the intent-to-treat group there were 13 penicillin-resistant, 38 penicillin-intermediate, and [redacted] *Streptococcus pneumoniae* isolates. In the microbiologically evaluable group there were 12 penicillin-resistant, 35 penicillin-intermediate, and [redacted] *Streptococcus pneumoniae* isolates. TABLE 8 shows the number of subjects from each study and TABLE 9 shows the number of levofloxacin treated subjects with penicillin or [redacted] nonsusceptible *Streptococcus pneumoniae* isolates for each study.

The following minimum inhibitory concentration (MIC) values were used as susceptibility criteria.

	MIC (µg/mL)	
Interpretation	Levofloxacin	Penicillin
Susceptible	≤ 2	≤ 0.06
Intermediate	4	0.1-1.0
Resistant	≥ 8	≥ 2

TABLE 8
Subjects with *Streptococcus pneumoniae* Isolates by Protocol

Sponsor / Protocol	Intent-to-Treat		Clinically Evaluable		Microbiologically Evaluable	
	Levofloxacin	Comparator	Levofloxacin[a]	Comparator	Levofloxacin[a]	Comparator
RWJPRI	271	45	235	35	235	34
LOFBIV-PCAP-001	155	–	140	–	140	–
K90-071	44	45	35	35	35	34
M92-075	46	–	37	–	37	–
LOFBIV-MULT-001	26	–	23	–	23	–
OMP	8	1	5	0	5	0
CAPSS-043[b]	7	–	4	–	4	–
CAPSS-056[b]	1	1	1	0	1	0
HMR	1	NA[d]	1	NA[d]	1	NA[d]
FF/93/355/02[c]	1	NA[d]	1	NA[d]	1	NA[d]
TOTAL	280	46	241	36	241	35

Note: A dash (–) represents not applicable since study did not include a comparator.
[a] The levofloxacin clinically evaluable group and levofloxacin microbiologically evaluable group are identical, every subject evaluable for clinical efficacy also is evaluable for microbiologic efficacy.
[b] Study is ongoing. Table includes only subjects with penicillin-intermediate or penicillin-resistant *S. pneumoniae* isolates.
[c] Includes only one subject who received levofloxacin 500 mg qd and had a penicillin-resistant isolate.
[d] Study had a comparator but data not included.

TABLE 9
Levofloxacin Treated Subjects with Penicillin or [redacted] Nonsusceptible *Streptococcus pneumoniae* Isolate

Sponsor / Protocol	Intent-to-Treat			Clinically/Microbiologically Evaluable		
	Penicillin		[redacted]	Penicillin		[redacted]
	Resistant	Intermediate	Resistant[a,b]	Resistant	Intermediate	Resistant[a,b]
RWJPRI	9	33	27	8	33	27
LOFBIV-PCAP-001	5	26	21	5	26	21
K90-071	1	4	2	0	4	2
M92-075	2	3	3	2	3	3
LOFBIV-MULT-001	1	0	1	1	0	1
OMP	3	5	–	3	2	–
CAPSS-043	2	5	–	2	2	–
CAPSS-056	1	0	–	1	0	–
HMR	1	–	–	1	–	–
FF/93/355/02	1	–	–	1	–	–
TOTAL	13	38	27	12	35	27

Note: A dash (–) represents not applicable.
[a] There were no isolates that had [redacted] MIC values in the intermediate category.
[b] Data regarding [redacted] susceptibility were used in efficacy summaries only from the four RWJPRI sponsored studies.

STUDY LOFBIV-PCAP-001

The information discussed below is from the sponsor's data. The Medical Officer has not yet reviewed these data. The Medical Officer's review may, therefore, have slightly different numbers of patients in each category.

This is a recently completed CAP trial and most of the data presented in this submission come from this trial. This was a noncomparative, multicenter study of levofloxacin in the treatment of CAP. Of the 655 subjects enrolled in the study, 155 subjects had *Streptococcus pneumoniae* isolates. There were 140 clinically and microbiologically evaluable (evaluable by sponsor) subjects with *S. pneumoniae.*

Streptococcus pneumoniae isolates from subjects evaluable for microbiological efficacy were tested to determine susceptibility to levofloxacin, penicillin, and [redacted]. TABLE 10 compares the cross-susceptibility of isolates to levofloxacin and penicillin. TABLE 11 compares levofloxacin and [redacted] cross-susceptibility.

TABLE 10
Cross-Susceptibility of *Streptococcus pneumoniae* Isolates to Levofloxacin and Penicillin by Subjects Evaluable for Microbiological Efficacy (Protocol LOFBIV-PCAP-001)

		Penicillin				
		S	I	R	U	
Levofloxacin	S	95	25	5	4	129
	I	0	0	0	0	0
	R	0	1	0	0	1
	U	0	0	0	10	10
		95	26	5	14	140

NOTE: S= Susceptible, I = Intermediate, R= Resistant, U = Unknown

TABLE 11

Le [redacted]

One hundred twenty-six subjects had *Streptococcus pneumoniae* isolates with susceptibility information for levofloxacin, penicillin, and ——. Of these 126 subjects, 95 (75%) had isolates that were susceptible to penicillin and 105 (83%) had isolates that were susceptible to —— all of these susceptible isolates were also susceptible to levofloxacin. All but one of the 126 isolates was susceptible to levofloxacin. This isolate had a levofloxacin MIC of 16 µg/mL, a —— MIC of ≥ 8 µg/mL, and a penicillin MIC of 1 µg/mL. It was, therefore, resistant to levofloxacin and —— and intermediate to penicillin. The subject with this levofloxacin resistant *Streptococcus pneumoniae* isolate was a clinical cure and the pathogen was considered eradicated at the posttherapy and poststudy evaluations.

Five (4%) subjects had isolates that showed resistance to penicillin and 21 (17%) had isolates that were resistant to —— Another 26 (21%) had isolates that were penicillin-intermediate. No susceptibility information was available for isolates from 10 subjects and only levofloxacin susceptibility information was available for an additional four subjects.

The posttherapy clinical and microbiological response rates of subjects infected with *S. pneumoniae* are presented in TABLE 12.

TABLE 12
Posttherapy Clinical and Microbiological Responses of *Streptococcus pneumoniae*
(Protocol LOFBIV-PCAP-001)

		Clinical Response			Microbiological Response		
Susceptibility	N[a]	Success[a,b]	Failure[a]	Unable to Evaluate[a]	Eradicated[a,b]	Persisted[a]	Unknown[a]
Penicillin							
Susceptible	95	91 (95.8%)	4 (4.2%)	0 (0.0%)	91 (95.8%)	4 (4.2%)	0 (0.0%)
Intermediate	26	26 (100.0%)	0 (0.0%)	0 (0.0%)	26 (100.0%)	0 (0.0%)	0 (0.0%)
Resistant	5	5 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)	0 (0.0%)	0 (0.0%)
Not Available	14	14 (100.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)	0 (0.0%)	0 (0.0%)
All Isolates	**140**	**136 (97.1%)**	**4 (2.9%)**	**0 (0.0%)**	**136 (97.1%)**	**4 (2.9%)**	**0 (0.0%)**

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.

[b] Clinical success = cured + improved. Microbiological eradication = eradicated + presumed eradicated.

[c] In this study, there were no *S. pneumoniae* isolates that had —— MICs in the intermediate category.

From the above table it can be seen that 97% of the subjects with *Streptococcus pneumoniae* isolates were clinical successes and had the isolate eradicated. There were 3% failures with persistent isolates. All four subjects who were considered clinical failures had microbiological persistence noted at the posttherapy evaluation. The admission and posttherapy isolates from all four of these subjects were susceptible to levofloxacin, however, one subject had an admission isolate that was —

Levofloxacin treatment was successful for all of the 31 subjects who had penicillin-intermediate or penicillin-resistant isolates at admission. Five subjects had CAP due to penicillin-resistant (MIC ≥ 2 µg/mL) *S. pneumoniae*. All of these five isolates were susceptible to levofloxacin and levofloxacin therapy was successful in all five cases

Fifteen subjects had isolates that were penicillin-intermediate or –resistant as well as — Four subjects had isolates that were resistant to both penicillin and — . Levofloxacin treatment of the infections of all four of these subjects was considered to be both clinically and microbiologically successful.

Subjects who completed the posttherapy visit (five to seven days after completion of therapy) with clinical success were evaluated again at a poststudy follow-up visit two to three weeks later. Subjects for whom an admission pathogen was eradicated at the posttherapy visit and reappeared in a culture obtained at the poststudy visit were considered to have a microbiological relapse. Subjects who were considered to have clinical relapse at the poststudy visit but did not have a specimen available for microbiological analysis were also considered to have microbiological relapse.

One hundred twenty-four evaluable subjects from whom *S. pneumoniae* was isolated at admission had a posttherapy clinical response of cured or improved and had microbiological response data available at the poststudy visit; of these, 121 (98%) of the subjects were considered to have microbiological eradication at the poststudy visit. Three (2%) subjects experienced microbiological relapse, two also had clinical relapse. None of the subjects who experienced relapse had *S. pneumoniae* isolates that were known to be nonsusceptible to penicillin, — , or levofloxacin.

Of the 241 subjects with *S. pneumoniae* isolates with known cross-susceptibility information for levofloxacin and penicillin, 190 (79%) had isolates that were susceptible to both drugs. Only one isolate was resistant to levofloxacin. Fifty-one (21%) subjects had isolates that were penicillin-intermediate (N=38) or resistant (N=13). All 13 isolates resistant to penicillin were susceptible to levofloxacin. Of the 38 subjects with isolates that were penicillin-intermediate, all but one subject (whose isolate was resistant to levofloxacin) had isolates that were susceptible to levofloxacin.

The posttherapy clinical and microbiological response rates of subjects with *Streptococcus pneumoniae* are shown in TABLE 15 for subjects evaluable for microbiological efficacy. Posttherapy clinical and microbiological response rates for all subjects evaluable were 98% success/eradicated and 2% failure/persisted.

Categorized by penicillin susceptibility, response was success/eradicated for 12 (100%) of the 12 subjects with penicillin-resistant isolates, 35 (100%) of 35 subjects with penicillin-intermediate isolates, 155 (97%) of 160 subjects with penicillin-susceptible isolates, and 34 (100%) of 34 subjects for whom penicillin susceptibility was not available. Five subjects failed therapy, including four subjects from the OFBIV-PCAP-001 study. Isolates from all of these five subjects were susceptible to levofloxacin and to penicillin.

TABLE 15
Posttherapy Clinical and Microbiological Responses of *Streptococcus pneumoniae*
(All Community-Acquired Pneumonia Trials)

		Clinical Response			Microbiological Response		
Susceptibility	N	Success[a]	Failure	Unknown	Eradicated	Persisted	Unknown
Penicillin[b]							
Susceptible	160	155 (96.9%)	5 (3.1%)	0 (0.0%)	155 (96.9%)	5 (3.1%)	0 (0.0%)
Intermediate	35	35 (100.0%)	0 (0.0%)	0 (0.0%)	35 (100.0%)	0 (0.0%)	0 (0.0%)
Resistant	12	12 (100.0%)	0 (0.0%)	0 (0.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)
Not Available	34	34 (100.0%)	0 (0.0%)	0 (0.0%)	34 (100.0%)	0 (0.0%)	0 (0.0%)
All Isolates[b]	**241**	**236 (97.9%)**	**5 (2.1%)**	**0 (0.0%)**	**236 (97.9%)**	**5 (2.1%)**	**0 (0.0%)**

Note: Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.

[a] Clinical success = cured + improved.

[b] Data represent isolates from seven studies. Susceptible, MIC ≤ 0.06 µg/mL; Intermediate, MIC 0.1-1.0 µg/mL; Resistant, MIC ≥ 2.0 µg/mL.

[c] Data represent isolates from four RWJPRI studies. Susceptible, MIC ≤ 0.25 µg/mL; Intermediate, MIC = 0.5 µg/mL; Resistant, MIC ≥ 1.0 µg/mL.

Based on the data from the seven clinical studies of CAP included in this submission, it appears that levofloxacin is able to eradicate *Streptococcus pneumoniae* in community-acquired pneumonia trials irrespective of susceptibility to either penicillin The Medical Officer's review is needed to determine if enough resistant isolates have been eradicated in clinical trials.

ALL CAP STUDIES COMBINED

The information discussed below is from the sponsor's data. The Medical Officer has not yet reviewed these data. The Medical Officer's review may, therefore, have slightly different numbers of patients in each category.

Isolates in this submission came from four RWJPRI trials (LOFBIV-PCAP-001, K90-071, M92-075, and LOFBIV-MULT-001), two OMP trials (CAPSS-043 and CAPSS-056), and one HMR trial (FF/93/355/02). Penicillin susceptibility information was available for both RWJPRI and non-RWJPRI studies. susceptibility data from only the RWJPRI studies are evaluated in support of the

Nearly all (271/280 = 97%) of the levofloxacin treated subjects with *Streptococcus pneumoniae* isolates came from studies sponsored by RWJPRI. All but one subject came from Johnson & Johnson sponsored (RWJPRI or OMP) studies. Of the 280 levofloxacin treated subjects (intent-to-treat) with *S. pneumoniae* isolates, 13 had isolates that were penicillin-resistant, 38 penicillin-intermediate, and Of the 241 levofloxacin treated subjects evaluable for microbiologic evaluation, 12 had isolates that were penicillin-resistant, 35 were penicillin-intermediate, and Of these 241 subjects, 235 (98%) were from RWJPRI trials, including 140 from the recently completed CAP trial, LOFBIV-PCAP-001. One penicillin-resistant subject (from study K90-071) was not evaluable clinically or microbiologically because the posttherapy visit was done outside of the window specified.

All the *Streptococcus pneumoniae* isolates found at admission were tested for susceptibility to levofloxacin, penicillin, and TABLE 13 displays the cross-susceptibility of isolates from all seven trails to penicillin and levofloxacin, while TABLE 14 displays the cross-susceptibility of isolates from the four RWJPRI studies to

TABLE 13
Cross-Susceptibility of *Streptococcus pneumoniae* Isolates to Levofloxacin and Penicillin at Study Admission (Intent-to-Treat)
(All Community-Acquired Pneumonia Trials)

		Penicillin[a]				
		S	I	R	U	
Levofloxacin	S	190[b]	37	13	3	243
	I	0	0	0	0	0
	R	0	1	0	0	1
	U	0	0	0	36	36
		190	38	13	14	280

[a] Susceptible, MIC ≤ 0.06 µg/mL; Intermediate, MIC 0.1-1.0 µg/mL; Resistant, MIC ≥ 2.0 µg/mL

[b] Twelve levofloxacin treated subjects had original ampicillin MIC values recorded as a surrogate for penicillin MIC values and did not have a subsequent repeat penicillin MIC value recorded. These ampicillin MIC values (three with values ≤ 1 µg/mL and nine with values ≤ 0.5 µg/ml) were used to classify these subjects as penicillin susceptible

S= Susceptible, I = Intermediate, R= Resistant, U = Unknown

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RECOMMENDATIONS

The sponsor should be notified of the following:

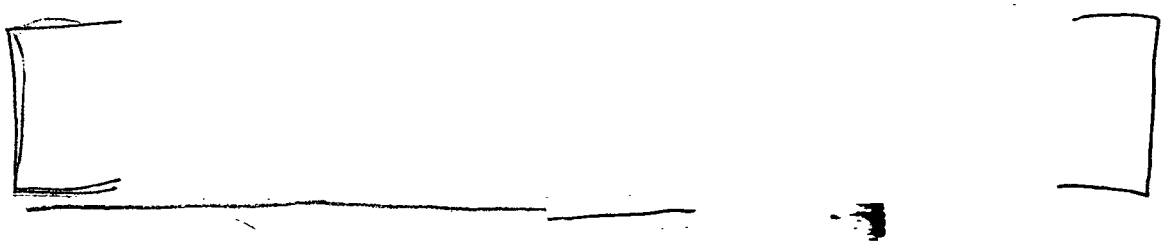
1. The addition of bacterial topoisomerase IV as a target of levofloxacin in the mechanism of action description is acceptable. This fact is now well known and topoisomerase IV is in the label of newer fluoroquinolones.

2. The addition of the words " both of which are type II" is acceptable since topoisomerase IV has been added and there are now two enzymes instead of only DNA gyrase.

3. The minor changes to the wording of the statement that fluoroquinolones differ in chemical structure and mode of action from other antimicrobials. Basically the addition of macrolides to this statement and the specification of penicillin are acceptable. Some fluoroquinolones even mention aminoglycosides in their label.

4. The addition of *Streptococcus pneumoniae* (including penicillin-resistant ——— or ——————————— strains).

   Sufficient evidence has been presented to demonstrate that levofloxacin retains its activity against penicillin non-susceptible strains of *Streptococcus pneumoniae*. The intermediate category, however, represents a buffer zone between susceptible and resistance. Intermediate results should be considered equivocal and the test repeated. The intermediate category has never been allowed in labeling. If the Medical Officer grants an indication for *S. pneumoniae* (including penicillin-resistant strains) then this organism may be listed as such in the first list (clinical efficacy shown) in the MICROBIOLOGY subsection. If this indication is not granted, then *Streptococcus pneumoniae* in the first listing must be qualified with the statement (penicillin-susceptible strains). A listing of *Streptococcus pneumoniae* without qualification would infer that all strains were tested in clinical trials. *Streptococcus pneumoniae* (penicillin-resistant strains) may then be added to the *in vitro* activity (list #2) list in the Microbiology subsection.



5. In order to complete the update of levofloxacin's label and to be consistent with the labeling of the other new fluoroquinolones the following revisions should also be made:

    1.1 *Enterococcus faecalis* should be listed as *Enterococcus faecalis* (many strains are only moderately susceptible)
    1.2 *Staphylococcus aureus* should be listed as *Staphylococcus aureus* (methicillin-susceptible strains)
    1.3 *Staphylococcus epidermidis* should be listed as *Staphylococcus epidermidis* (methicillin-susceptible strains)
    1.4 *Citrobacter diversus* should be listed as *Citrobacter (diversus) koseri*
    1.5 ——————————should be deleted since it is now classified under the other listed species.
    1.6 *Enterobacter agglomerans* should be listed as *Pantoea (Enterobacter) agglomerans.*

The Microbiology subsection should, therefore, read as follows:

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs of this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these micrcorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms
Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus (Group C/F)
Streptococcus (Group G)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffi
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes
Pantoea (Enterobacter) agglomerans
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringes

Susceptibility Tests

This section is satisfactory as written. No changes have been made.

/S/
Peter A. Dionne
Microbiologist HFD-590

CONCURRENCES:

HFD-590/Div Dir /S/ Signature 6/10/99 Date
HFD-590/TLMicr Signature 4/28/99 Date

CC:
HFD-590/Original NDA # 20634/SEI-008
HFD-590/Division File
HFD-590/Micro/PDionne
HFD-590/MO/LSacks
HFD-520/Pharm/SHundley
HFD-590/Chem/GHolbert
HFD-590/CSO/RAnderson

JUN 10 1999

MICROBIOLOGY REVIEW

DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS (HFD-590)

NDA #: 20-635/SEI-007

REVIEWER:	Peter A. Bionne
CORRESPONDENCE DATE:	31-MAR-99
CDER DATE:	01-APR-99
REVIEW ASSIGN DATE:	06-APR-99
REVIEW COMPLETE DATE:	23-APR-99

SPONSOR: The R.W. Johnson Pharmaceutical Research Institute
920 Route 202 South
P.O. Box 300
Raritan, New Jersey 08869-0602

CONTACT PERSON: Mary Ellen Zamstein
Principal Regulatory Scientist, Regulatory Affairs
Phone Number: (908) 704-4198

SUBMISSION REVIEWED: Revisions to Microbiology and Indications and Usage sections of package insert (addition of penicillin-resistant and ——— *Streptococcus pneumoniae* to approved community-acquired pneumonia claim).

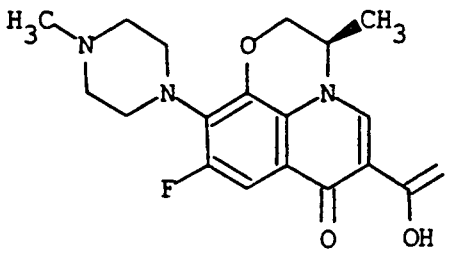
DRUG CATEGORY: Antimicrobial: Fluoroquinolone

INDICATIONS: Sinusitis, ABECB, CAP, Skin and Skin Structure, Complicated UTI, Acute pyelonephritis, Uncomplicated UTI

DOSAGE FORM: Levofloxacin Injection 25 mg/mL, ———

DRUG PRODUCT NAME

PROPRIETARY: LEVAQUIN® Injection
NONPROPRIETARY/USAN: Levofloxacin injection
CODE: RWJ-25213-097
CHEMICAL NAME: (-)-(S)-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
STRUCTURAL FORMULA:



Molecular Formula: $C_{18}H_{20}FN_3O_4$ Molecular Weight: 361.38

SUPPORTING DOCUMENTS: NDA 20-634—LEVAQUIN Tablets

BACKGROUND:

The applicant wishes to make revisions to the MICROBIOLOGY subsection and the INDICATIONS AND USAGE section of their package insert. The main revision that they are requesting is the addition of the following wording "(including penicillin-resistant)[redacted]" after *Streptococcus pneumoniae* in their approved community-acquired pneumonia indication and the addition of this wording to list #1 (clinical efficacy shown) in the MICROBIOLOGY subsection.

All of the pre-clinical microbiology information submitted in this supplement has previously been submitted in supplement 006 dated December 17, 1998. This supplement was for the addition of the above wording to list #2 (*in vitro* activity) in the MICROBIOLOGY subsection. The first part of this review is, therefore, identical to the review for supplement 006, which was dated January 12, 1999.

CONCLUSIONS:

The supplemental application is approvable from the microbiological viewpoint when changes are made to the MICROBIOLOGY subsection of the package insert. The reviewing Medical Officer will need to decide whether enough evidence has been presented to grant an indication for resistant *Streptococcus pneumoniae*. This will determine whether or not these organisms are listed in the MICROBIOLOGY subsection in list #1 (clinical efficacy) or in list #2 (*in vitro* activity only). The changes needed should be sent to the sponsor. These revisions are listed as recommendations at the end of this review on pages 22-25.

TABLE OF CONTENTS

INTRODUCTION

The applicant has requested the following revisions to the microbiology section of their package insert:

- Add bacterial topoisomerase IV as a target of levofloxacin in the mechanism of action description.
- Add the words "both of which are type II" since topoisomerase IV has been added and there are now two enzymes instead of only DNA gyrase.
- Make minor changes to the wording of the statement that fluoroquinolones differ in chemical structure and mode of action from other antimicrobials. Basically they want to add macrolides to this statement and specify penicillin (
- Add *Streptococcus pneumoniae* (including penicillin-resistant strains)

REVISIONS TO MECHANISM OF ACTION AND RESISTANCE STATEMENT

The applicant has submitted one reference (1) to substantiate the addition of topoisomerase IV as a target for the drug. This fact is now well known and topoisomerase IV is in the label of newer fluoroquinolones. It may be added to levofloxacin's label.

The addition of to the statement about chemical structure and mode of action is also correct and some other fluoroquinolones even mention aminoglycosides. These changes may be made.

ACTIVITY OF LEVOFLOXACIN AGAINST PENICILLIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

The following data have been submitted to demonstrate that levofloxacin is active against penicillin-intermediate and –resistant strains. Table 1 summarizes the nine studies submitted.

TABLE 1

Summary of *In vitro* Activity of Levofloxacin against *Streptococcus pneumoniae*

Penicillin Susceptibility	No. Isolates	MIC Test Method[a]	MIC Range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)	Country Year (Ref.)
Pen-S	2699	BMD	≤0.004->8	0.5	1.0	99.9	0.0	0.1	USA
Pen-I	915		≤0.004->8	0.5	1.0	99.6	0.1	0.3	1998
Pen-R	538		0.015-2.0	0.5	1.0	100.0	0.0	0.0	(2)
All	9145	E-test	≤0.002->32	1.0	2.0	97.3	2.1	0.6	USA
Pen-S	6081		0.008->32	1.0	2.0	97.4	2.2	0.4	1997
Pen-I	1817		0.032->32	1.0	2.0	96.9	1.9	1.2	(3)
Pen-R	1247		≤0.002->32	1.0	2.0	97.1	1.8	1.1	
All	690	BMD	0.25->16	NA[b]	1.0	NA	NA	NA	USA
Pen-S	154		0.25-1	0.5	1.0	100	0.0	0.0	1997
Pen-I	150		0.5-16	0.5	1.0	NA	NA	NA	(4)
Pen-R	100		0.5-1	0.5	1.0	100	0.0	0.0	
Pen-S	53	AD	0.25-2.0	1.0	2.0	100	0.0	0.0	USA
Pen-I	84		0.25-2.0	1.0	2.0	100	0.0	0.0	1997
Pen-R	74		0.25-2.0	2.0	2.0	100	0.0	0.0	(5)
All	142	BMD	0.5->8.0	1.0	2.0	NA	NA	NA	USA
Pen-S	123		0.5-2.0	1.0	2.0	100	0.0	0.0	1996
Pen-I-R	19		1.0->8.0	1.0	2.0	NA	NA	NA	(6)
Pen-S	23	AD	0.5-2.0	1.0	1.0	100	0.0	0.0	USA
Pen-R	15		0.5-1.0	1.0	1.0	100	0.0	0.0	1996 (7)
Pen-S	962	BMD	0.12-8.0	0.5	1.0	NA	NA	NA	Canada
Pen-I	91		0.25-8.0	1.0	1.0	NA	NA	NA	1996
Pen-R	36		0.5-8.0	0.5	1.0	NA	NA	NA	(8)
Pen-S	60	AD	NA	0.5	2.0	100	0.0	0.0	South
Pen-I	60		NA	0.5	1.0	100	0.0	0.0	Africa
Pen-R	60		NA	0.5	2.0	100	0.0	0.0	1996 (9)
Pen-S	28	AD	0.39-3.13	0.78	1.56	NA	NA	NA	Japan 1997
Pen-R[c]	21		0.20-1.56	0.78	1.56	NA	NA	NA	(10)

[a] BMD = Broth microdilution; AD = Agar Dilution
[b] NA = data were not available
[c] Pen-S = MIC <0.05 µg/mL; Pen-R = MIC >0.05 µg/mL

These studies demonstrate that levofloxacin MIC_{90} values are unchanged for penicillin-susceptible, -intermediate, and –resistant strains within a study, with the exception of the South African study in which the MIC_{90} for penicillin-intermediate isolates was 1.0 µg/mL compared to MIC_{90} values of 2.0 µg/mL for penicillin-susceptible and –resistant strains. A small increase in the percentage of isolates resistant to levofloxacin was seen in the penicillin-intermediate and penicillin-resistant isolates compared with penicillin-susceptible isolates in one 1997 study conducted in the United States, but this trend was not seen in other studies. Levofloxacin activity remains the same irrespective of the country of origin of the isolates or the *in vitro* susceptibility testing method.

The *in vitro* activity of levofloxacin against *Streptococcus pneumoniae* isolates obtained from subjects treated with levofloxacin during clinical trials that evaluated the efficacy and safety of levofloxacin in the treatment of Community Acquired Pneumonia is summarized in TABLE 2.

TABLE 2
Distribution of Levofloxacin MIC Values (µg/mL) for Levofloxacin-Treated Subjects with Baseline Pathogen *Streptococcus pneumoniae* from Community Acquired Pneumonia Clinical Trials

	No. of Isolates with an MIC (µg/mL)								Levofloxacin	
No. of isolates	<0.25	0.25	0.5	1.0	2.0	4.0	8.0	16	MIC_{50}	MIC_{90}
Pen-S (190)	1	8	27	122	32	0	0	0	1.0	2.0
Pen-I (38)	0	1	10	24	2	0	0	1	1.0	1.0
Pen-R (13)	0	0	3	8	2	0	0	0	1.0	2.0

These data demonstrate that all isolates were susceptible to levofloxacin with the exception of one penicillin-intermediate isolate (penicillin MIC of 1.0 µg/mL) that was levofloxacin-resistant with a levofloxacin MIC of 16 µg/mL. MIC_{50} values remained at 1.0 µg/mL for all isolates regardless of penicillin susceptibility. MIC_{90} values were 2.0 µg/mL for penicillin-susceptible and penicillin-resistant isolates, and 1.0 µg/mL for penicillin-intermediate strains. Since there is a one-dilution error in the method these values are all equivalent.

Barry et al. (11) evaluated the *in vitro* activity of levofloxacin against 654 isolates of *S. pneumoniae*, of which 80 were penicillin-intermediate and 64 were resistant to penicillin. The MIC_{90} for all isolates was 2.0 µg/mL and none was resistant to levofloxacin, while only one strain was levofloxacin-intermediate with a MIC of 4 µg/mL.

In another study (12) of 100 isolates of *S. pneumoniae* (60 penicillin-susceptible, 21 penicillin-intermediate, and 19-penicillin-resistant), none of the isolates was resistant to levofloxacin and the MIC_{90} was 1.0 µg/mL. In comparison, 43% of these isolates were resistant to erythromycin and 11-38% were resistant to expanded spectrum cephalosporins. Erythromycin and cephalosporin susceptibility decreased as penicillin susceptibility decreased.

Plouffe (13) demonstrated that 99.2% of 499 bacteremic isolates of *Streptococcus pneumoniae* collected from Ohio hospitals during 1991-1994 were susceptible to levofloxacin. Of the 39 isolates with penicillin MICs ≥0.12 µg/mL, 38 were susceptible to levofloxacin, as were four of the five penicillin-resistant isolates.

Lister and Edward (14) evaluated the bactericidal activity of levofloxacin against five penicillin-susceptible and five penicillin-resistant strains of *Streptococcus pneumoniae* using an *in vitro* pharmacokinetic model of infection. Levofloxacin was bactericidal against all ten strains with viable counts decreasing 4-6 logs by 6 hours.

George and Morrissey (15) compared the bactericidal activity of levofloxacin with other fluoroquinolones and cefotaxime against penicillin-susceptible, -intermediate, and –resistant strains of *S. pneumoniae*. Levofloxacin was the most bactericidal fluoroquinolone tested and its activity was similar for all strains regardless of susceptibility to penicillin.

Vesga and Craig (16) used murine model of a thigh infection to study the *in vivo* activity of levofloxacin against one penicillin-intermediate and six penicillin-resistant strains of *Streptococcus pneumoniae* in two strains of mice. Levofloxacin was successful against the penicillin-intermediate and –resistant strains. They predicted that based on the 24-hour AUC/MIC required for efficacy and the AUC obtained in patients dosed with 500 mg of levofloxacin once daily, levofloxacin should provide effective therapy for penicillin-resistant *S. pneumoniae*.

ACTIVITY OF LEVOFLOXACIN AGAINST *STREPTOCOCCUS PNEUMONIAE*

WITHHOLD 3 PAGE(S)

TABLE 7
Summary of *In Vitro* Activity of Penicillin, Macrolides, and Levofloxacin Against *Streptococcus pneumoniae*

Penicillin Status	Macrolide						Levofloxacin						Country Test Method[a]	Reference
	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)	No. Isolates	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	S (%)	I (%)	R (%)		
All	9138	0.125	6.0	80.9	0.9	18.2	9145	1.0	2.0	97.3	2.1	0.6	USA/E-test	3
Pen-S	6094	0.125	0.25	94.9	1.1	4.0	6081	1.0	2.0	97.4	2.2	0.4		
Pen-I	1803	0.125	64	63.5	1.7	34.8	1817	1.0	2.0	96.9	1.9	1.2		
Pen-R	1241	2.0	>256	38.9	1.0	60.1	1247	1.0	2.0	97.1	1.8	1.1		
Pen-S	53	0.03	2.0	NA	NA	NA	53	1.0	2.0	NA	NA	NA	USA/AD	5
Pen-I	84	0.25	4.0	NA	NA	NA	84	1.0	2.0	NA	NA	NA		
Pen-R	74	2.0	>64	NA	NA	NA	74	2.0	2.0	NA	NA	NA		
All	142	0.125	0.25	NA	NA	NA	142	1.0	2.0	NA	NA	NA	USA/BMD	6
Pen-S	123	0.125	0.25	NA	NA	NA	123	1.0	2.0	NA	NA	NA		
Pen-I-R	19	0.125	4.0	NA	NA	NA	19	1.0	2.0	NA	NA	NA		
All[b]	100	≤0.5	>0.5	NA	NA	43.0	100	0.5	1.0	NA	NA	0.0	USA/BMD	12
Pen-S	963	0.12	0.12	98	0.4	1.6	962	0.5	1.0	99.8	0.0	0.2	Canada/BMD	8
Pen-I	91	0.25	0.5	88	2.2	9.8	91	1.0	1.0	97.8	1.1	1.1		
Pen-R	36	0.25	2.0	75	8.3	16.7	36	1.0	1.0	97.2	0.0	2.8		
All (S = 52.7%)	294	NA	>32	37.4	NA	NA	294	NA	1.0	98.3	NA	NA	Japan/BMD	19

[a] BMD = broth microdilution; AD = agar dilution
[b] S = 69, I = 21, R = 19
NA = information not available

DATA FROM CLINICAL STUDIES

This supplement has one new study LOFBIV-PCAP-001 and looks at other Phase 3 community-acquired pneumonia (CAP) studies in which levofloxacin was dosed at 500 mg qd for 7 to 14 days. The sponsor is trying to find enough penicillin-resistant *Streptococcus pneumoniae* isolates to get an indication for CAP caused by penicillin-resistant *S. pneumoniae*. Efficacy data are integrated from all subjects with CAP from whom *S. pneumoniae* was isolated at admission from the following R.W. Johnson Pharmaceutical Research Institute (RWJPRI) studies: LOFBIV-PCAP-001 (recent study), and studies K90-071, M92-075, and LOFBIV-MULT-001 which were included as part of the original NDA.

Due to difficulty encountered in the RWJPRI studies in enrolling subjects with penicillin-resistant *S. pneumoniae*, data from subjects with penicillin-resistant or penicillin-intermediate isolates of *S. pneumoniae* who were enrolled on or before June 12, 1998 in two ongoing non-IND CAP trials, CAPSS-043 and CAPSS-056, also are included in this submission. These studies were sponsored by Ortho-McNeil Pharmaceutical (OMP). In addition, data from one 500 mg qd levofloxacin treated subject with penicillin-resistant *S. pneumoniae* from a Heochst Marion Roussel (HMR) CAP trial FF/93/355/02 were included in this submission. Information regarding [redacted] is presented only for the four RWJPRI sponsored trials since [redacted] *S. pneumoniae* isolates were found in adequate numbers in these studies alone.

Approximately 2400 subjects with CAP were enrolled across the seven studies. Approximately 1800 received levofloxacin 500 mg qd. Efficacy data are presented for 280 levofloxacin treated subjects with *S. pneumoniae* isolates. All but nine isolates came from RWJPRI sponsored studies. In the intent-to-treat group there were 13 penicillin-resistant, 38 penicillin-intermediate, [redacted] *Streptococcus pneumoniae* isolates. In the microbiologically evaluable group there were 12 penicillin-resistant, 35 penicillin-intermediate, and [redacted] *Streptococcus pneumoniae* isolates. TABLE 8 shows the number of subjects from each study and TABLE 9 shows the number of levofloxacin treated subjects with penicillin or [redacted] nonsusceptible *Streptococcus pneumoniae* isolates for each study.

The following minimum inhibitory concentration (MIC) values were used as susceptibility criteria.

	MIC (µg/mL)		
Interpretation	Levofloxacin	[redacted]	Penicillin
Susceptible	≤ 2		≤ 0.06
Intermediate	4		0.1-1.0
Resistant	≥ 8		≥ 2

TABLE 8
Subjects with *Streptococcus pneumoniae* Isolates by Protocol

Sponsor / Protocol	Intent-to-Treat		Clinically Evaluable		Microbiologically Evaluable	
	Levofloxacin	Comparator	Levofloxacin[a]	Comparator	Levofloxacin[a]	Comparator
RWJPRI	271	45	235	35	235	34
LOFBIV-PCAP-001	155	–	140	–	140	–
K90-071	44	45	35	35	35	34
M92-075	46	–	37	–	37	–
LOFBIV-MULT-001	26	–	23	–	23	–
OMP	8	1	5	0	5	0
CAPSS-043[b]	7	–	4	–	4	–
CAPSS-056[b]	1	1	1	0	1	0
HMR	1	NA[d]	1	NA[d]	1	NA[d]
FF/93/355/02[c]	1	NA[d]	1	NA[d]	1	NA[d]
TOTAL	280	46	241	36	241	35

Note: A dash (–) represents not applicable since study did not include a comparator.
[a] The levofloxacin clinically evaluable group and levofloxacin microbiologically evaluable group are identical, every subject evaluable for clinical efficacy also is evaluable for microbiologic efficacy.
[b] Study is ongoing. Table includes only subjects with penicillin-intermediate or penicillin-resistant *S. pneumoniae* isolates.
[c] Includes only one subject who received levofloxacin 500 mg qd and had a penicillin-resistant isolate.
[d] Study had a comparator but data not included.

TABLE 9
Levofloxacin Treated Subjects with Penicillin or [redacted] Nonsusceptible *Streptococcus pneumoniae* Isolate

Sponsor / Protocol	Intent-to-Treat			Clinically/Microbiologically Evaluable		
	Penicillin		[redacted]	Penicillin		[redacted]
	Resistant	Intermediate	Resistant[a,b]	Resistant	Intermediate	Resistant[a,b]
RWJPRI	9	33	27	8	33	27
LOFBIV-PCAP-001	5	26	21	5	26	21
K90-071	1	4	2	0	4	2
M92-075	2	3	3	2	3	3
LOFBIV-MULT-001	1	0	1	1	0	1
OMP	3	5	–	3	2	–
CAPSS-043	2	5	–	2	2	–
CAPSS-056	1	0	–	1	0	–
HMR	1	–	–	1	–	–
FF/93/355/02	1	–	–	1	–	–
TOTAL	13	38	27	12	35	27

Note: A dash (–) represents not applicable.
[a] There were no isolates that had [redacted] MIC values in the intermediate category.
[b] Data regarding [redacted] susceptibility were used in efficacy summaries only from the four RWJPRI sponsored studies.

STUDY LOFBIV-PCAP-001

The information discussed below is from the sponsor's data. The Medical Officer has not yet reviewed these data. The Medical Officer's review may, therefore, have slightly different numbers of patients in each category.

This is a recently completed CAP trial and most of the data presented in this submission come from this trial. This was a noncomparative, multicenter study of levofloxacin in the treatment of CAP. Of the 655 subjects enrolled in the study, 155 subjects had *Streptococcus pneumoniae* isolates. There were 140 clinically and microbiologically evaluable (evaluable by sponsor) subjects with *S. pneumoniae*.

Streptococcus pneumoniae isolates from subjects evaluable for microbiological efficacy were tested to determine susceptibility to levofloxacin, penicillin, and [redacted] TABLE 10 compares the cross-susceptibility of isolates to levofloxacin and penicillin. TABLE 11 compares levofloxacin and [redacted] cross-susceptibility.

TABLE 10
Cross-Susceptibility of *Streptococcus pneumoniae* Isolates to Levofloxacin and Penicillin by Subjects Evaluable for Microbiological Efficacy (Protocol LOFBIV-PCAP-001)

		Penicillin				
		S	I	R	U	
Levofloxacin	S	95	25	5	4	129
	I	0	0	0	0	0
	R	0	1	0	0	1
	U	0	0	0	10	10
		95	26	5	14	140

NOTE: S= Susceptible, I = Intermediate, R= Resistant, U = Unknown

TABLE 11

[redacted]

One hundred twenty-six subjects had *Streptococcus pneumoniae* isolates with susceptibility information for levofloxacin, penicillin, and [redacted] Of these 126 subjects, 95 (75%) had isolates that were susceptible to penicillin and 105 (83%) had isolates that were susceptible to [redacted] all of these susceptible isolates were also susceptible to levofloxacin. All but one of the 126 isolates was susceptible to levofloxacin. This isolate had a levofloxacin MIC of 16 µg/mL, a [redacted] MIC of ≥ 8 µg/mL, and a penicillin MIC of 1 µg/mL. It was, therefore, resistant to levofloxacin and [redacted] and intermediate to penicillin. The subject with this levofloxacin resistant *Streptococcus pneumoniae* isolate was a clinical cure and the pathogen was considered eradicated at the posttherapy and poststudy evaluations.

Five (4%) subjects had isolates that showed resistance to penicillin and 21 (17%) had isolates that were resistant to [redacted] Another 26 (21%) had isolates that were penicillin-intermediate. No susceptibility information was available for isolates from 10 subjects and only levofloxacin susceptibility information was available for an additional four subjects.

The posttherapy clinical and microbiological response rates of subjects infected with *S. pneumoniae* are presented in TABLE 12.

TABLE 12
Posttherapy Clinical and Microbiological Responses of *Streptococcus pneumoniae*
(Protocol LOFBIV-PCAP-001)

		Clinical Response			Microbiological Response		
Susceptibility	N[a]	Success[a,b]	Failure[a]	Unable to Evaluate[a]	Eradicated[a,b]	Persisted[a]	Unknown[a]
Penicillin							
Susceptible	95	91 (95.8%)	4 (4.2%)	0 (0.0%)	91 (95.8%)	4 (4.2%)	0 (0.0%)
Intermediate	26	26 (100.0%)	0 (0.0%)	0 (0.0%)	26 (100.0%)	0 (0.0%)	0 (0.0%)
Resistant	5	5 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)	0 (0.0%)	0 (0.0%)
Not Available	14	14 (100.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)	0 (0.0%)	0 (0.0%)
Erythromycin[c]							
Susceptible	105	102 (97.1%)	3 (2.9%)	0 (0.0%)	102 (97.1%)	3 (2.9%)	0 (0.0%)
Resistant	21	20 (95.2%)	1 (4.8%)	0 (0.0%)	20 (95.2%)	1 (4.8%)	0 (0.0%)
Not Available	14	14 (100.0%)	0 (0.0%)	0 (0.0%)	14 (100.0%)	0 (0.0%)	0 (0.0%)
All Isolates	**140**	**136 (97.1%)**	**4 (2.9%)**	**0 (0.0%)**	**136 (97.1%)**	**4 (2.9%)**	**0 (0.0%)**

[a] Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.
[b] Clinical success = cured + improved. Microbiological eradication = eradicated + presumed eradicated.
[c] In this study, there were no *S. pneumoniae* isolates that had [redacted] MICs in the intermediate category.

From the above table it can be seen that 97% of the subjects with *Streptococcus pneumoniae* isolates were clinical successes and had the isolate eradicated. There were 3% failures with persistent isolates. All four subjects who were considered clinical failures had microbiological persistence noted at the posttherapy evaluation. The admission and posttherapy isolates from all four of these subjects were susceptible to levofloxacin, however, one subject had an admission isolate that was

Levofloxacin treatment was successful for all of the 31 subjects who had penicillin-intermediate or penicillin-resistant isolates at admission. Five subjects had CAP due to penicillin-resistant (MIC ≥ 2 µg/mL) *S. pneumoniae*. All of these five isolates were susceptible to levofloxacin and levofloxacin therapy was successful in all five cases.

[

]

Fifteen subjects had isolates that were penicillin-intermediate or -resistant as well as Four subjects had isolates that were resistant to both penicillin and Levofloxacin treatment of the infections of all four of these subjects was considered to be both clinically and microbiologically successful.

Subjects who completed the posttherapy visit (five to seven days after completion of therapy) with clinical success were evaluated again at a poststudy follow-up visit two to three weeks later. Subjects for whom an admission pathogen was eradicated at the posttherapy visit and reappeared in a culture obtained at the poststudy visit were considered to have a microbiological relapse. Subjects who were considered to have clinical relapse at the poststudy visit but did not have a specimen available for microbiological analysis were also considered to have microbiological relapse.

One hundred twenty-four evaluable subjects from whom *S. pneumoniae* was isolated at admission had a posttherapy clinical response of cured or improved and had microbiological response data available at the poststudy visit; of these, 121 (98%) of the subjects were considered to have microbiological eradication at the poststudy visit. Three (2%) subjects experienced microbiological relapse, two also had clinical relapse. None of the subjects who experienced relapse had *S. pneumoniae* isolates that were known to be nonsusceptible to penicillin, erythromycin, or levofloxacin.

ALL CAP STUDIES COMBINED

The information discussed below is from the sponsor's data. The Medical Officer has not yet reviewed these data. The Medical Officer's review may, therefore, have slightly different numbers of patients in each category.

Isolates in this submission came from four RWJPRI trials (LOFBIV-PCAP-001, K90-071, M92-075, and LOFBIV-MULT-001), two OMP trials (CAPSS-043 and CAPSS-056), and one HMR trial (FF/93/355/02). Penicillin susceptibility information was available for both RWJPRI and non-RWJPRI studies. susceptibility data from only the RWJPRI studies are evaluated in support of the

Nearly all (271/280 = 97%) of the levofloxacin treated subjects with *Streptococcus pneumoniae* isolates came from studies sponsored by RWJPRI. All but one subject came from Johnson & Johnson sponsored (RWJPRI or OMP) studies. Of the 280 levofloxacin treated subjects (intent-to-treat) with *S. pneumoniae* isolates, 13 had isolates that were penicillin-resistant, 38 penicillin-intermediate, and Of the 241 levofloxacin treated subjects evaluable for microbiologic evaluation, 12 had isolates that were penicillin-resistant, 35 were penicillin-intermediate, and 27 were Of these 241 subjects, 235 (98%) were from RWJPRI trials, including 140 from the recently completed CAP trial, LOFBIV-PCAP-001. One penicillin-resistant subject (from study K90-071) was not evaluable clinically or microbiologically because the posttherapy visit was done outside of the window specified.

All the *Streptococcus pneumoniae* isolates found at admission were tested for susceptibility to levofloxacin, penicillin, and TABLE 13 displays the cross-susceptibility of isolates from all seven trails to penicillin and levofloxacin, while TABLE 14 displays the cross-susceptibility of isolates from the four RWJPRI studies to

TABLE 13
Cross-Susceptibility of *Streptococcus pneumoniae* Isolates to Levofloxacin and Penicillin at Study Admission (Intent-to-Treat)
(All Community-Acquired Pneumonia Trials)

		Penicillin[a]				
		S	I	R	U	
Levofloxacin	S	190[b]	37	13	3	243
	I	0	0	0	0	0
	R	0	1	0	0	1
	U	0	0	0	36	36
		190	38	13	14	280

[a] Susceptible, MIC ≤ 0.06 µg/mL; Intermediate, MIC 0.1-1.0 µg/mL; Resistant, MIC ≥ 2.0 µg/mL

[b] Twelve levofloxacin treated subjects had original ampicillin MIC values recorded as a surrogate for penicillin MIC values and did not have a subsequent repeat penicillin MIC value recorded. These ampicillin MIC values (three with values ≤ 1 µg/mL and nine with values ≤ 0.5 µg/ml) were used to classify these subjects as penicillin susceptible

S= Susceptible, I = Intermediate, R= Resistant, U = Unknown

Of the 241 subjects with *S. pneumoniae* isolates with known cross-susceptibility information for levofloxacin and penicillin, 190 (79%) had isolates that were susceptible to both drugs. Only one isolate was resistant to levofloxacin. Fifty-one (21%) subjects had isolates that were penicillin-intermediate (N=38) or resistant (N=13). All 13 isolates resistant to penicillin were susceptible to levofloxacin. Of the 38 subjects with isolates that were penicillin-intermediate, all but one subject (whose isolate was resistant to levofloxacin) had isolates that were susceptible to levofloxacin.

The posttherapy clinical and microbiological response rates of subjects with *Streptococcus pneumoniae* are shown in TABLE 15 for subjects evaluable for microbiological efficacy. Posttherapy clinical and microbiological response rates for all subjects evaluable were 98% success/eradicated and 2% failure/persisted.

Categorized by penicillin susceptibility, response was success/eradicated for 12 (100%) of the 12 subjects with penicillin-resistant isolates, 35 (100%) of 35 subjects with penicillin-intermediate isolates, 155 (97%) of 160 subjects with penicillin-susceptible isolates, and 34 (100%) of 34 subjects for whom penicillin susceptibility was not available. Five subjects failed therapy, including four subjects from the LOFBIV-PCAP-001 study. Isolates from all of these five subjects were susceptible to levofloxacin and to penicillin.

TABLE 15
Posttherapy Clinical and Microbiological Responses of *Streptococcus pneumoniae*
(All Community-Acquired Pneumonia Trials)

		Clinical Response			Microbiological Response		
Susceptibility	N	Success[a]	Failure	Unknown	Eradicated	Persisted	Unknown
Penicillin[b]							
Susceptible	160	155 (96.9%)	5 (3.1%)	0 (0.0%)	155 (96.9%)	5 (3.1%)	0 (0.0%)
Intermediate	35	35 (100.0%)	0 (0.0%)	0 (0.0%)	35 (100.0%)	0 (0.0%)	0 (0.0%)
Resistant	12	12 (100.0%)	0 (0.0%)	0 (0.0%)	12 (100.0%)	0 (0.0%)	0 (0.0%)
Not Available	34	34 (100.0%)	0 (0.0%)	0 (0.0%)	34 (100.0%)	0 (0.0%)	0 (0.0%)
All Isolates[b]	**241**	**236 (97.9%)**	**5 (2.1%)**	**0 (0.0%)**	**236 (97.9%)**	**5 (2.1%)**	**0 (0.0%)**

Note: Values represent the number of subjects. Numbers shown in parentheses are percentages for that category.

[a] Clinical success = cured + improved.

[b] Data represent isolates from seven studies. Susceptible, MIC ≤ 0.06 µg/mL; Intermediate, MIC 0.1-1.0 µg/mL; Resistant, MIC ≥ 2.0 µg/mL.

[c] Data represent isolates from four RWJPRI studies. Susceptible, MIC ≤ 0.25 µg/mL; Intermediate, MIC = 0.5 µg/mL; Resistant, MIC ≥ 1.0 µg/mL.

Based on the data from the seven clinical studies of CAP included in this submission, it appears that levofloxacin is able to eradicate *Streptococcus pneumoniae* in community-acquired pneumonia trials irrespective of susceptibility to either penicillin The Medical Officer's review is needed to determine if enough resistant isolates have been eradicated in clinical trials.

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RECOMMENDATIONS

The sponsor should be notified of the following:

1. The addition of bacterial topoisomerase IV as a target of levofloxacin in the mechanism of action description is acceptable. This fact is now well known and topoisomerase IV is in the label of newer fluoroquinolones.

2. The addition of the words " both of which are type II" is acceptable since topoisomerase IV has been added and there are now two enzymes instead of only DNA gyrase.

3. The minor changes to the wording of the statement that fluoroquinolones differ in chemical structure and mode of action from other antimicrobials. Basically the addition of macrolides to this statement and the specification of penicillin are acceptable. Some fluoroquinolones even mention aminoglycosides in their label.

4. The addition of *Streptococcus pneumoniae* (including penicillin-resistant strains).

   Sufficient evidence has been presented to demonstrate that levofloxacin retains its activity against penicillin non-susceptible strains of *Streptococcus pneumoniae*. The intermediate category, however, represents a buffer zone between susceptible and resistance. Intermediate results should be considered equivocal and the test repeated. The intermediate category has never been allowed in labeling. If the Medical Officer grants an indication for *S. pneumoniae* (including penicillin-resistant strains) then this organism may be listed as such in the first list (clinical efficacy shown) in the MICROBIOLOGY subsection. If this indication is not granted, then *Streptococcus pneumoniae* in the first listing must be qualified with the statement (penicillin-susceptible strains). A listing of *Streptococcus pneumoniae* without qualification would infer that all strains were tested in clinical trials. *Streptococcus pneumoniae* (penicillin-resistant strains) may then be added to the *in vitro* activity (list #2) list in the Microbiology subsection.

5. In order to complete the update of levofloxacin's label and to be consistent with the labeling of the other new fluoroquinolones the following revisions should also be made:

    1.1 *Enterococcus faecalis* should be listed as *Enterococcus faecalis* (many strains are only moderately susceptible)
    1.2 *Staphylococcus aureus* should be listed as *Staphylococcus aureus* (methicillin-susceptible strains)
    1.3 *Staphylococcus epidermidis* should be listed as *Staphylococcus epidermidis* (methicillin-susceptible strains)
    1.4 [redacted] should be listed as *Citrobacter (diversus) koseri*
    1.5 *Acinetobacter anitratus* should be deleted since it is now classified under the other listed species.
    1.6 *Enterobacter agglomerans* should be listed as *Pantoea (Enterobacter) agglomerans.*

The Microbiology subsection should, therefore, read as follows:

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram-positive microorganisms
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs of this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown.**

Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC's) of 2 µg/mL or less against most (≥90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms
Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus (Group C/F)
Streptococcus (Group G)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffi
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes
Pantoea (Enterobacter) agglomerans
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringes

Susceptibility Tests

This section is satisfactory as written. No changes have been made.

/S/
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CONCURRENCES:

HFD-590/Div Dir_ /S/ _Signature 6/10/99 Date
HFD-590/TLMicro_____ _Signature 4/29/99 Date

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HFD-590/Chem/GHolbert
HFD-590/CSO/RAnderson