OTHER CLINICAL STUDIES OF CAP

Studies K90-071, M92-075, and LOFBIV-MULT-001 were submitted and reviewed in the original NDA and were the clinical studies forming the basis for approval of the CAP indication in the original NDA. For further details on the review of these studies, please see the Medical Officer's Review of the Original NDA 20-634 and NDA 20-635 for the indication of CAP.

Four additional studies contributed patients to the group of patients with CAP due to PRSP or PISP (Table 44). Three of these studies are ongoing non-IND studies of levofloxacin in the treatment of CAP being conducted by Ortho McNeil Pharmaceutical, Inc. (studies CAPSS-043, CAPSS-056, and CAPSS-018). The fourth study (Study FF/93/355/02) is a CAP study that was conducted by Hoescht Marion Roussel (now Aventis). This study (Study FF/93/355/02) contributed a single patient to the group of levofloxacin-treated patients with PRSP.

Table 44. Additional Studies Providing Patients with Community-Acquired Pneumonia due to PRSP or PISP

Study No. (Location)	Design	Regimen (Duration)	Number of CAP Patients with	
			PRSP	PISP
CAPSS-018 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone and Erythromycin (IV) to Amoxicillin/Clav and Clarithromycin (7-14 days)	0 (levo) 3 (cef)	1 (levo) 4 (cef)
CAPSS-043 (USA)	open label, non-comparative (non-IND)	Levo IV or PO (7-14 days)	6 (levo)	14 (levo)
CAPSS-056 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone/ Azithromycin(PO) (10 days)	2 (levo) 1 (cef/az)	1 (levo) 1 (cef/az)
FF/93/355/02 (Europe, South Africa, Argentina)	double-blind, randomized, comparative	Levo PO vs Amox/Clav (7-10 days)	1 (levo) 0 (am/cl)	0 (levo) 0 (am/cl)

The Study design and endpoints for each of these four studies will be briefly described. In general, the studies required patients to exhibit radiographic and clinical signs and symptoms of community-acquired pneumonia. Patients underwent a microbiologic evaluation in search of the microbial etiology of their underlying pneumonia. Patients received therapy with levofloxacin at 500 mg daily or an equivalent dose adjusted for renal insufficiency. Patients were treated for 7 to 14 days. Following the admission assessment, patients were evaluated

again during therapy, Post-Therapy and in some of the studies, again at the Post-Study timepoint.

While there was variation across the studies with regards to the number and timing of post-therapy assessments, the primary data (case report forms) for all of the patients with CAP due to PRSP or PISP was available for review. Review of the case report forms for all of the patients allowed a standardized approach to the determination of evaluability and clinical response to therapy.

All cases of CAP due to PRSP or PISP were reviewed at the level of the case report forms using the criteria that are discussed in the section of this document entitled, Integrated Summary of Efficacy for LEVAQUIN® for the Treatment of Community-Acquired Pneumonia due to PRSP. For a discussion of the cases of CAP due to PRSP or PISP from Studies CAPSS-043, CAPSS-056, CAPSS-018, and FF/93/355/02, please refer to the Integrated Summary

Study CAPSS-018

CAPSS-018 is an on-going non-IND study being conducted by Ortho McNeil Pharmaceutical, Inc. It is a randomized, multicenter, open-label study comparing the safety and efficacy of levofloxacin vs. ceftriaxone and erythromycin followed by amoxicillin/clavulanate in the treatment of patients with severe community-acquired pneumonia in adults. The study is being conducted in the US.

The design of the clinical study is very similar to Study LOFBIV-PCAP-001. The protocol-specified study evaluations include an admission visit, an on-therapy visit, a Post Therapy visit (5-7 days post-therapy), and a 1 Month Post-Therapy visit. At the admission visit, eligible patients must demonstrate clinical and radiographic evidence of pneumonia and must have at least 3 of the American Thoracic Criteria for hospital admission. At admission and at the efficacy evaluations, patients are evaluated clinically, radiographically, and with a microbiologic evaluation. Patients are to receive therapy for 7 to 14 days. The planned enrollment is 212 patients to yield 79 evaluable patients per treatment arm. The efficacy data from the study will be evaluated in intent-to-treat, clinically evaluable, and microbiologically evaluable populations. Clinical response and microbiological response will be determined. Safety will be analyzed by examining the incidence, severity, and types of adverse events.

MO Comment: Study CAPSS-018 is very similar in design to Study LOFBIV-PCAP-001. It involves am entirely US study population. One notable difference of

CAPSS-018 compared to LOFBIV-PCAP-001 is that CAPSS-018 is specifically designed to enroll patients with serious pneumonia requiring hospitalization.

Study CAPSS-043

Study CAPSS-043 is non-IND study being conducted by Ortho McNeil Pharmaceutical, Inc. It is a multicenter, non-comparative study to assess the safety and efficacy of levofloxacin in the treatment of community-acquired pneumonia in adults. In addition, one of the protocol-stated objectives of the study is to evaluate the efficacy of levofloxacin in the treatment of CAP due to PRSP and to compare the efficacy of levofloxacin in the treatment of CAP due to PRSP vs. PSSP. The study is being conducted in the US at 600 to 750 centers. The planned enrollment for the study is 6210 patients.

In order to be eligible for study enrollment, patients must have clinical and radiographic evidence of pneumonia. Patients admitted to study are treated with levofloxacin 500 mg IV or PO daily. Patients are evaluated at an On-Therapy assessment (Days 3-5) and at a single Post-Therapy assessment scheduled for 2 to 7 days following the completion of therapy. At the Admission and Post-Therapy assessments, patients undergo clinical, radiographic, and microbiological evaluations. Efficacy analyses will include measurement of clinical response and microbiological response in the intent-to-treat, clinically evaluable, and microbiologically evaluable populations. The safety analysis will involve the examination of the incidence, severity, and type of adverse reactions.

MO Comment: Other than the timing and number of post-therapy assessments, this US study is similar in design to LOFBIV-PCAP-001.

Study CAPSS-056

CAPSS-056 is a non-IND study being conducted by Ortho McNeil Pharmaceutical, Inc. It is a multicenter, open-label, randomized study to compare the safety and efficacy of levofloxacin to azithromycin in the treatment of moderate to severe community-acquired pneumonia in adults. The study is being conducted in the US. The planned study enrollment is 198 patients for 74 evaluable patients per treatment group.

Patients must have clinical and radiographic evidence of pneumonia to be eligible for study enrollment. Patients must also have a Fine risk score of 71 to 130 (Fine MJ, NEJM 1997:336 (4); 243-250). Eligible patients will be randomized to receive either levofloxacin 500 mg IV or PO daily vs. azithromycin 500 mg IV q24H for a minimum of 2 days and ceftriaxone 1 g

IV q24H for the first 2 days of therapy after which patients may be transitioned to oral azithromycin 500 mg PO daily at the investigators discretion. Patients are to receive a minimum of 10 days of therapy. Patients are to undergo clinical, radiographic, and microbiological assessments at admission and at the 2 to 7 day Post-Therapy assessment. Patients will also be evaluated on-therapy between Days 3 to 5. Clinical response and microbiological response will be analyzed for the intent-to-treat, and evaluable populations. Safety will be evaluated by monitoring the incidence, severity, and type of adverse events that occur during the study.

Study FF/93/355/02

Study FF/93/355/02 is a multinational study of CAP in adults conducted by Hoescht Marion Roussell. The study is randomized, multicenter, double-blind, double-dummy comparative study designed to evaluate the safety and efficacy of levofloxacin 500 mg PO daily vs. levofloxacin 500 mg PO BID vs. amoxicillin/clavulanate 500/125 mg PO TID. Patients are to receive 7 to 10 days of therapy. The study enrolled a total of 518 patients.

In order to be eligible for the study patients must have clinical and radiographic evidence of community-acquired pneumonia. Following admission, patients were assessed at one or 2 on-therapy assessments and at two post-therapy assessments scheduled for 2 to 5 days and 14-21 days after completing therapy. Patients were evaluated clinically, radiographically, and microbiologically at admission and at each of the post-therapy assessments. The clinical and microbiologic response rates were measured in an intent-to-treat and evaluable populations. The type, incidence, and severity of adverse events were also summarized.

> **MO Comment:** In Study FF/93/355/02 levofloxacin was studied at two different dosages. Only the data derived form the use of the US approved dosage of levofloxacin for the treatment of CAP were eligible for supporting the efficacy of levofloxacin in the treatment of CAP.

INTEGRATED SUMMARY OF EFFICACY FOR LEVAQUIN® FOR THE TREATMENT OF COMMUNITY-ACQUIRED PNEUMONIA DUE TO PRSP

Introduction

The Applicant identified a subset of patients from their clinical studies of community-acquired pneumonia in adults who had either PISP or PRSP isolated at the time of admission. This group of patients represented all of the levofloxacin-treated patients with PRSP or PISP in any one of their 8 clinical studies of CAP. The Applicant included data on all cases of CAP due to PRSP or PISP from all of the clinical efficacy studies of levofloxacin at the dose of 500 mg daily for the treatment of CAP that were conducted by RWJPRI, Ortho-McNeil Pharmaceutical, Inc., Hoescht Marion Roussel (now Aventis), or Daiichi Pharmaceuticals. At the request of the Agency, all patients from these studies who received comparator therapy and had either PRSP or PISP as their admission isolate were also identified.

The approach to the information that is submitted in support of this efficacy supplement will be to first briefly present information on the microbiological susceptibility of *S. pneumoniae* from surveillance studies and also from the clinical isolates of *S. pneumoniae* from the Applicant's clinical studies. Second, selected pharmacokinetic information on levofloxacin will be briefly presented. Then, the clinical data in support of the Applicant's proposed claim (CAP due to PRSP) will be presented.

The approach to the clinical data supporting the application involves three main elements. First, briefly reviewing the efficacy data for levofloxacin for the treatment of community-acquired pneumonia (of all causes) from the original NDA studies. Second, an examination of the efficacy rates for levofloxacin in the treatment of CAP due to *S. pneumoniae*. Third, an examination of the efficacy results for the subset of levofloxacin- and comparator-treated patients with CAP due to PRSP and PISP (note that only 4 of the 8 studies were comparative studies – resulting in fewer comparator treated patients with PRSP and PISP).

Microbiology

In their Application, RWJPRI provided a summary of the *in vitro* activity of levofloxacin against *S. pneumoniae* from 9 published reports. Their summary table is reproduced below (Table 45). The MIC_{90} values from these studies for levofloxacin against PSSP, PISP, and PRSP range from 1 to 2 mcg/mL.

Table 45: Summary of *In Vitro* Activity of Levofloxacin Against *Streptococcus pneumoniae*

Penicillin Susceptibility[a]	No. Isolates	MIC Test Method[b]	MIC Range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/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	(6)
All	9145	Etest	≤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	(7)
Pen-R	1247		≤0.002->32	1.0	2.0	97.1	1.8	1.1	
All	690	BMD	0.25->16	NA[c]	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	(8)
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	(9)
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	(10)
Pen-S	23	AD	0.5-2	1.0	1.0	100	0.0	0.0	USA
Pen-R	15		0.5-1	1.0	1.0	100	0.0	0.0	1996
									(11)
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	(12)
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
									(13)
Pen-S[d]	28	AD	0.39-3.13	0.78	1.56	NA	NA	NA	Japan
									1997
Pen-R[d]	21		0.20-1.56	0.78	1.56	NA	NA	NA	(14)

[a] S = penicillin-susceptible, MIC ≤0.06 mcg/mL; I = penicillin-intermediate, MIC 0.12-1.0 mcg/mL; R = penicillin-resistant, MIC ≥ 2 mcg/mL
[b] BMD = broth microdilution; AD = Agar dilution
[c] NA = data were not available
[d] Pen-S = MIC <0.05 mcg/mL; Pen-R = MIC >0.05 mcg /mL
(Adapted from Applicant's Table 4 from NDA 20-634 SE1-008, Vol. 25.2, p. 19)

MO Comment: More recently, a publication from the Canadian Bacterial Surveillance Network reports the prevalence of pneumococci with reduced susceptibility to fluoroquinolones as 1.7% (2.9% in the adult population) for the years

1997 and 1998 combined (fluoroquinolone resistance was defined as an MIC ≥ 4 mcg/mL for ciprofloxacin).[5] This level of resistance represents an increase from the 0% rate of fluoroquinolone resistance observed during the years 1988 and 1993. The report also found that pneumococci with reduced susceptibility to fluoroquinolones were more likely to be resistant to other antimicrobial agents including the following: penicillin, relative risk (RR) of 5 (95% CI 2.5 to 10); trimethoprim-sulfamethoxazole, RR = 3.9 (95% CI 2.2 to 7.0); tetracycline, RR = 2.7 (95% CI 1.2 to 5.8).[5]

In their application, RWJPRI also tabulated the MIC values for the *Streptococcus pneumoniae* isolates from the 8 clinical trials that are the subject of this supplemental NDA (Table 46).

Table 46: Distribution of Levofloxacin MIC Values (µg/mL) for Intent-to-Treat Levofloxacin Subjects[a] from CAP Clinical Trials with *Streptococcus pneumoniae* at Admission

Penicillin Susceptibility (No. of Subjects with Isolates)	Levofloxacin MIC (µg/mL)								Levofloxacin	
	<0.25	0.25	0.5	1.0	2.0	4.0	8.0	16	MIC_{50}	MIC_{90}
Pen-S (N=190)[b]	1	8	27	122	32	0	0	0	1.0	2.0
Pen-I (N=38)[c]	0	1	10	24	2	0	0	1	1.0	1.0
Pen-R (N=13)[d]	0	0	3	8	2	0	0	0	1.0	2.0

[a] Levofloxacin dosed at 500 mg q.d.
[b] Includes penicillin-susceptible *S. pneumoniae* subjects from four RWJPRI trials (LOFBIV-PCAP-001, LOFBIV-MULT-001, K90-071, M92-075)
[c] Includes penicillin-intermediate *S. pneumoniae* subjects from four RWJPRI and two OMP trials (CAPPS-043, CAPSS-056).
[d] Includes penicillin-resistant *S. pneumoniae* subjects from four RWJPRI, two OMP, and one HMR trials (HMR trial # FF/93/355/02).
RWJPRI = R.W. JOHNSON Pharmaceutical Research Institute, OMP = Ortho McNeil Pharmaceutical, Inc.
HMR = Hoescht Marion Roussel
(Adapted from Applicant's Table 5 from NDA 20-634 SE1-008, Vol. 25.2, p. 20)

MO Comment: The MIC_{90} values observed from the clinical isolates from these studies are consistent with the MIC_{90} values for PSSP, PISP, and PRSP from published reports.[6-14]

In their current submission, the Applicant provided cross-tabulations of antimicrobial resistance for the combinations of levofloxacin and penicillin, levofloxacin and erythromycin, and penicillin and erythromycin for the *S. pneumoniae* isolates from all of their CAP clinical trials (Table 47). The cross-tabulation of levofloxacin and penicillin resistance from their clinical isolates reveals one levofloxacin-resistant *S. pneumoniae* isolate. This levofloxacin-resistant isolate was intermediately resistant to penicillin (a brief clinical summary for this patient is provided in the MO Comment that follows). The

remaining 243 isolates for which susceptibility results were available were all levofloxacin-susceptible. Thirty-seven of these 243 isolates were PISP and 13 were PRSP.

MO Comment: The patient with CAP due to levofloxacin-resistant PISP was Pt. No. 3026 from Study LOFBIV-PCAP-001. He was a 43-year-old male with a history of renal insufficiency who presented with clinical and radiographic evidence of pneumonia and *S. pneumoniae* cultured from sputum. The MICs for his *S. pneumoniae* isolate were, levofloxacin MIC = 16 mcg/mL and penicillin MIC = 1 mcg/mL. He was treated as an outpatient and received levofloxacin 500 mg po QD for Days 1 and 2 and then his dose was reduced based on a calculated creatinine clearance (in accordance with the product labeling) to levofloxacin 250 mg po QD for Days 3 through 10. (His serum creatinine from admission was 5.0 mg/dL.) He was scored as a clinical cure and microbiological eradication at both the Post-Therapy visit (6 days post-therapy) and the Post-Study visit (28 days post-therapy).

Table 47: Cross-Susceptibility of *S. pneumoniae* Isolates (from Study Admission) to Levofloxacin, Penicillin, and Erythromycin, Intent-to-Treat Subjects from all CAP Studies.

a. Levofloxacin and Penicillin

		Penicillin [a]				
		S	I	R	U	
Levofloxacin	S	190 [b]	37	13	3	243
	I	0	0	0	0	0
	R	0	1 [c]	0	0	1
	U	0	0	0	36	36
		190	38	13	39	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 (3 with values ≤1.0 µg/mL and 9 with values ≤0.5 µg/mL) were used to classify these subjects as penicillin susceptible.

[c] Pt. No. 3026 from Study LOFBIV-PCAP-001 (See MO Comment on the prior page)

S=susceptible; I=intermediate; R=resistant; U=susceptibility unknown.

Adapted From Applicant's Table 18. p.31, NDA20-634 SE1-008, Vol. 25.24

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b. Levofloxacin and Erythromycin

		Erythromycin [a]				
		S	I	R	U	
Levofloxacin	S	204 [b]	0	26	4	234
	I	0	0	0	0	0
	R	0	1	0	0	1
	U	0	0	0	36	36
		204	0	27	40	271

[a] Susceptible, MIC ≤0.25 µg/mL; intermediate, MIC=0.5 µg/mL; resistant, MIC ≥1.0 µg/mL.
[b] Twelve subjects (3 from study LOFBIV-MULT-001, 5 from K90-071, and 4 from M92-075) had erythromycin MIC values ≤0.5 µg/mL. Confirmatory MIC testing could not be done on these isolates so they were counted as susceptible.

S=susceptible; I=intermediate; R=resistant; U=susceptibility unknown.

Adapted From Applicant's Table 19. p.31, NDA20-634 SE1-008, Vol. 25.24

Table 47: (Continued) Cross-Susceptibility of *S. pneumoniae* Isolates (from Study Admission) to Levofloxacin, Penicillin, and Erythromycin, Intent-to-Treat Subjects from all CAP Studies.

c. Penicillin and Erythromycin

		Erythromycin [a]				
		S	I	R	U	
Penicillin [d]	S	180 [b, c]	0	9	1	190
	I	20	0	13	5	38
	R	5	1	6	2	13
	U	0	0	0	39	39
		205	0	28	47	280

[a] Susceptible, MIC ≤0.25 µg/mL; intermediate, MIC=0.5 µg/mL; resistant, MIC ≥1.0 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 (3 with values ≤1.0 µg/mL and 9 with values ≤0.5 µg/mL) were used to classify these subjects as penicillin susceptible.
[c] Twelve subjects (3 from study LOFBIV-MULT-001, 5 from K90-071, and 4 from M92-075) had erythromycin MIC values ≤0.5 µg/mL. Confirmatory MIC testing could not be done on these isolates so they were counted as susceptible.
[d] Susceptible, MIC ≤0.06 µg/mL; intermediate, MIC 0.1-1.0 µg/mL; resistant, MIC ≥2.0 µg/mL.

S=susceptible; I=intermediate; R=resistant; U=susceptibility unknown.

Adapted From Applicant's Table 10. p.32, NDA20-634 SE1-008, Vol. 25.24

Pharmacokinetics

Based on the pharmacokinetic information provided in the LEVAQUIN® product labeling, serum levels following either single or multiple doses of oral or intravenous levofloxacin are shown in Table 48. Studies of the levels of levofloxacin in lung tissue found concentrations 2 to 5 times higher than in plasma (range 2.4 to 11.3 mcg/mL) after a single oral dose of 500 mg of levofloxacin.[15]

Table 48: Pharmacokinetic Parameters (+/- S.D.) for Levofloxacin

Regimen	C_{max} (mcg/mL)	T_{max} (h)	AUC (mcg·h/mL)	CL/F[1] (mL/min)	$t_{½}$ (h)
Single Dose					
500 mg po [2]	5.1 +/- 0.8	1.3 +/- 0.6	47.9 +/- 6.8	178 +/- 28	6.3 +/- 0.6
500 mg iv [2]	6.2 +/- 1.0	1.0 +/- 0.1	48.3 +/- 5.4	175 +/- 20	6.4 +/- 0.7
Multiple Dose					
500 mg po [2]	5.7 +/- 1.4	1.1 +/- 0.4	47.5 +/- 6.7	175 +/- 25	7.6 +/- 1.6
500 mg iv [2]	6.4 +/- 0.8	ND	54.6 +/- 11.1	158 +/- 29	7.0 +/- 0.8
500 mg or 250 mg q24h iv, patients with bacterial infection [3]	8.7 +/- 4.0[4]	ND	72.5 +/- 51.2[4]	154 +/- 72	ND

[1] clearance/bioavailability
[2] healthy males 18-53 years of age
[3] 500 mg q 48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin
[4] dose normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling
Pharamacokinetic values are from the levofloxacin product labeling

The current LEVAQUIN® product labeling and the NCCLS guidelines provide the following "susceptibility" breakpoints for levofloxacin for *Streptococcus pneumoniae* (Table 49).[15, 16]

Table 49: LEVAQUIN® MIC Susceptibility Interpretations for *S. pneumoniae*

LEVAQUIN® MIC (mcg/ml)	Interpretation
≤ 2	Susceptible (S)
4	Intermediate (I)
≥ 8	Resistant (R)

Animal models of infection have been used to evaluate the activity of levofloxacin against *S. pneumoniae* in experimentally induced animal infections. In a murine model of lower respiratory tract infection, levofloxacin demonstrated activity against *S. pneumoniae* based on a reduction in log_{10}cfu/g in lung tissue.[17] Other animal studies have been performed to model infection secondary to PRSP and have predicted that of levofloxacin would be efficacious against PRSP based on the AUC/MIC ratio that is likely to be required for efficacy.[18]

Efficacy of LEVAQUIN® in the treatment of Community-Acquired Pneumonia and CAP Secondary to *Streptococcus pneumoniae* – Original NDA Studies

Three clinical studies were submitted in the original NDA that supported the approval of LEVAQUIN® for Community-Acquired Pneumonia and resulted in the inclusion of *Streptococcus pneumoniae* among the indicated pathogens. The 3 studies were K90-071 an open-label, randomized, active control study of patients with CAP; M92-075, an open-label,

non-comparative study of patients with CAP; and study LOFBIV-MULT-001, a multi-infection study which enrolled some patients with CAP. Following a brief overview of the study designs, the patient demographics and summary tables of efficacy results for the 2 major CAP studies (K90-071 and M92-075) will be presented. The efficacy results presented are based upon the Medical Officer's Review of the original NDAs for LEVAQUIN® (tablets and injection).[19]

In Study K90-071, patients were randomized to receive either levofloxacin or a cephalosporin-based regimen. The dosages used were levofloxacin 500 mg IV or PO QD or ceftriaxone 1 to 2 grams IV daily or cefuroxime 500 mg PO BID with the option to add either IV or PO erythromycin 0.5 to 1 gram QID to the cephalosporin arm. An amendment to the protocol dated October 5, 1993, allowed comparator patients to receive doxycycline if they were unable to tolerate erythromycin. (Note: the protocol also allowed levofloxacin to be dosed as 500 mg BID. The 17 patients who received this dose are not included in the efficacy analyses presented). The study enrolled a total of 596 patients. Two hundred and seventy-eight patients received levofloxacin 500 mg daily and 295 received the comparator regimen.

Study M92-075 was a non-comparative, open-label study of levofloxacin 500 mg IV or PO daily. A total of 264 patients were enrolled and received levofloxacin.

The demographic and baseline characteristics of the patients in the levofloxacin and comparator arms of Study K90-071 are comparable. Comparison of the characteristics of the patients in Study M92-075 reveals a relatively similar patient population to the patients in Study K90-071. In both studies, 16 to 17% of the patient's disease at baseline were graded as severe and approximately 40% of the patients were hospitalized (Table 50).

Table 50: Patient Demographics and Baseline Characteristics, From the Applicant's Clinically Evaluable Population

Characteristic	Study K90-071				Study M92-075	
	Levofloxacin (N = 226)		Ceftriaxone/Cefuroxime (N = 230)		Levofloxacin (N = 234)	
Sex	n	(%)	n	(%)	n	(%)
Male	125	(55)	124	(54)	132	(56)
Female	101	(45)	106	(46)	102	(44)
Race						
Caucasian	147	(65)	151	(66)	195	(83)
Black	74	(33)	75	(33)	34	(15)
Hispanic	5	(2)	2	(<1)	4	(2)
Other	0	(0)	2	(<1)	1	(<1)
Age (years)						
≤ 45	107	(47)	108	(47)	97	(41)
45-64	71	(31)	61	(27)	64	(27)
≥ 65	48	(21)	61	(27)	73	(32)
Mean +/- SD	49 +/- 18	-	50 +/- 19	-	52 +/- 18	-
Range	19-87	-	18-93	-	18-93	-
Severity						
Severe	36	(16)	37	(16)	40	(17)
Mild/Moderate	190	(84)	193	(84)	194	(83)
Status						
Inpatient	104	(46)	96	(42)	88	(38)
Outpatient	122	(54)	134	(58)	146	(62)

Table Adapted from Tables 12.1.4 and 12.1.3.C from pp. 272 and 357 of the Medical Officer's Review of Original NDA 20-634 and NDA 20-635

The Medical Officer's rates for Post-Therapy clinical cure in the clinically evaluable population of Study K90-071 were 62% for levofloxacin and 46% for the ceftriaxone/cefuroxime regimen. The clinical success rates (cured + improved) for levofloxacin were 95% compared to a clinical success rate of 83% for the ceftriaxone/cefuroxime-based regimen (Table 51). The 95% confidence interval for the difference in clinical success rates (ceftriaxone/cefuroxime arm minus levofloxacin arm) was (-18.6, -6.2). In the non-comparative CAP study, M92-075, the levofloxacin clinical cure rate was 52% and the clinical success rate was 93%.

Table 51: Clinical Response Rates for Studies K90-071 and M92-075 as per the Reviewing Medical Officer, Clinically Evaluable Population

Post-Therapy Clinical Response														
	Levofloxacin 500 mg QD							Ceftriaxone/Cefuroxime						
Study	N	Cured		Improved		Failed		N	Cured		Improved		Failed	
		n	%	n	%	n	%		n	%	n	%	n	%
K90-071	207	129	(62)	68	(33)	10	(5)	226	105	(46)	82	(36)	39	(17)
M92-075	203	105	(52)	83	(41)	15	(7)	-	-	-	-	-	-	-
Combined	410	234	(57)	151	37	25	(6)	-	-	-	-	-	-	-

Post-Therapy Clinical Success										
	Levofloxacin 500 mg QD					Ceftriaxone/Cefuroxime				
Study	N	Success		Failure		N	Success		Failure	
		n	%	n	%		n	%	n	%
K90-071	207	197	(95)	10	(5)	226	187	(83)	39	(17)
M92-075	203	188	(93)	15	(7)	-	-	-	-	-
Combined	410	385	(94)	25	(6)	-	-	-	-	-

The MO's microbiological eradication rates for the microbiologically evaluable population in Study K90-071 were 96% for Levofloxacin compared to 81% for the ceftriaxone/cefuroxime regimen (Table 52). The microbiological eradication rate from the non-comparative CAP (M92-075) study was 94%.

Table 52: Microbiological Response Rates for Studies K90-071 and M92-075 in The Microbiologically Evaluable Population as per the Reviewing Medical Officer

	Study Therapy					
	Levofloxacin 500 mg QD			Ceftriaxone/Cefuroxime		
Study	N	Eradicated[1]		N	Eradicated[1]	
		n	%	N	n	%
K90-071	119	114	(96)	152	123	(81)
M92-075	161	151	(94)	-	-	-
K90-071 and M92-075 Combined	280	265	(95)	-	-	-

[1] For the purposes of this table, Eradication includes both documented eradication and presumed eradication. Note: A patient who was a clinical success and not able to provide an appropriate specimen for culture at the test-of-cure visit is scored as a presumed eradication.

The clinical success rates for patients with *Streptococcus pneumoniae* as their admission isolate and for other selected pathogens were analyzed from the original NDA clinical studies of CAP (K90-071 and M92-075). In the analyses that follow, *S. pneumoniae* isolates were not stratified by degree of penicillin susceptibility. In studies K90-071 and M92-075, there

were a total of 3 PRSP isolates and 7 PISP isolates in the levofloxacin-treated patients and 0 PRSP and 4 PISP isolates in the ceftriaxone/cefuroxime arm of Study K90-071. Hence, the results tabulated for *S. pneumoniae* represent primarily PSSP (Table 53).

The clinical success rates for *S. pneumoniae* in the Medical Officer's clinically evaluable population of Study K90-071 were 97% for levofloxacin compared to 85% for the ceftriaxone/cefuroxime regimen. The *S. pneumoniae* clinical success rate for levofloxacin in Study M92-075 was 95%. In Studies K90-071 and M92-075, approximately 25-30% of the patients who had *S. pneumoniae* as their admission isolate were bacteremic.

Table 53: Clinical Response Rates for Studies K90-71 and M92-075 as per the Reviewing Medical Officer

Study Pathogen	Study Therapy					
	Levofloxacin 500 mg QD			Ceftriaxone/Cefuroxime		
	N	Eradicated[1]		N	Eradicated[1]	
		n	%		n	%
Study K90-071						
S. pneumoniae	29	28	(97)	34	29	(85)
H. influenzae	27	27	(100)	24	15	(63)
M. catarrhalis	7	6	(86)	6	5	(83)
Study M92-075						
S. pneumoniae	34	32	(94)	-	-	-
H. influenzae	29	26	(90)	-	-	-
M. catarrhalis	11	10	(91)	-	-	-
Studies K90-071 and M92-075 Combined						
S. pneumoniae	63	60	(95)	-	-	-
H. influenzae	56	53	(95)	-	-	-
M. catarrhalis	18	16	(89)	-	-	-

[1] For the purposes of this table, Eradication includes both documented eradication and presumed eradication. Note: A patient who was a clinical success and not able to provide an appropriate specimen for culture at the test-of-cure visit is scored as a presumed eradication.

Summary of Applicant's Efficacy Analysis for CAP due to *S. Pneumoniae*

As the basis for their current application, the Applicant assembled data from all of their clinical studies of CAP in order to gather all of the data on the clinical performance of levofloxacin against PSSP, PISP, and PRSP. Table 54 is reproduced from Applicant's current submission and represents the clinical and microbiologic response rates stratified by degree of penicillin-sensitivity for the cumulative population of subjects evaluable for microbiologic efficacy. The data presented have been collected from a total of 3,908 subjects enrolled in CAP studies of which 3,055 were treated with levofloxacin. Five hundred and thirteen of these patients had *S. pneumoniae* isolated on culture. Of these 513 isolates, 18 were PRSP and 49 were PISP. (Note: the results in Table 54 are for the 241

microbiologically evaluable patients available at the time of the initial NDA submission in March 1999 at which time 13 PRSP and 38 PISP patients had been identified.) The composite data are presented in the absence of comparator data because 4 of the 8 studies from which the data were drawn did not include comparators.

MO Comment: The numbers 13 PRSP and 38 PISP cases represent the total number of patients identified with CAP due to PRSP or PISP prior to the additional cases submitted to the Agency on September 20, 1999. The number of cases in Table 54 is less than the total number of cases because the table represents only the microbiologically evaluable cases.

Table 54: Post-Therapy Clinical and Microbiologic Responses of Subjects With *S. pneumoniae* Isolates Stratified by Susceptibility to Penicillin: Levofloxacin Subjects Evaluable for Microbiologic Efficacy (All Community-Acquired Pneumonia Trials) (per Applicant)

		Clinical Response			Microbiologic Response		
Penicillin Susceptibility[a]	N	Success[b]	Failure	Unable to Evaluate	Eradicated[c]	Persisted	Unknown
Susceptible	160	15 (96.9)	5 (3.1)	0 (0.0)	155 (96.9)	5 (3.1)	0 (0.0)
Intermediate	35	3 (100.0)	0 (0.0)	0 (0.0)	35 (100.0)	0 (0.0)	0 (0.0)
Resistant	12	1 (100.0)	0 (0.0)	0 (0.0)	12 (100.0)	0 (0.0)	0 (0.0)
Not available	34	3 (100.0)	0 (0.0)	0 (0.0)	34 (100.0)	0 (0.0)	0 (0.0)
Total	**241**	**23 (97.9)**	**5 (2.1)**	**0 (0.0)**	**236 (97.9)**	**5 (2.1)**	**0 (0.0)**

Note: Values represent number (%) of subjects.

[a] Susceptible, MIC ≤0.06 µg/mL; intermediate, MIC 0.1-1.0 µg/mL; resistant, MIC ≥2.0 µg/mL.

[b] Clinical response 'success' includes both cured and improved cases.

[c] For the purposes of this table microbiological response "eradication" includes both eradication and presumed eradication.

Note: The additional patients submitted 20 September 1999 are not included in this table

Applicant's Table 13 from NDA 20-634 SE1-008, vol. 25.24 p. 36

Note: the results in Table 59 are for the 241 microbiologically evaluable patients available at the time of the initial NDA submission in March 1999 at which time 13 PRSP and 38 PISP patients had been identified.

MO Comment: From the results in Table 54, the rates of penicillin resistance observed in the microbiologically evaluable population with *S. pneumoniae* isolates from the 8 clinical trials can be approximated. For the 207 patients for whom penicillin susceptibility was known, 12 had PRSP and 35 had PISP. Therefore, in this composite study population the rates for PRSP and PISP are approximately 6% (12/207) and 17% (35/207), respectively. Note that some studies allowed patients to be enrolled that had failed prior therapy and were suspected or known to have CAP due to PRSP. Hence, the study population may be somewhat enriched for patients with CAP due to PRSP.

Clinical Efficacy Data on LEVAQUIN® for the Treatment of PRSP and PISP

The Applicant assembled data from all of their CAP studies that used levofloxacin at the dose of 500 mg daily. From this group of 8 clinical trials, patients with penicillin-resistant

Streptococcus pneumoniae (PRSP) and with penicillin-intermediate *Streptococcus pneumoniae* (PISP) were identified. Four of the 8 studies were open-label, non-comparative studies (Table 55). One of the non-comparative studies was initiated specifically to gather data on levofloxacin for the treatment of resistant pneumococci and [redacted], Study LOFBIV-PCAP-001 (previously reviewed in this document).

Following the initial submission of this sNDA, an additional 5 levofloxacin-treated PRSP CAP patients and 11 levofloxacin-treated PISP CAP patients were identified from ongoing CAP trials (CAPSS-018, CAPSS-043, and CAPSS-056). These additional patients were submitted to the Agency on September 20, 1999. With the addition of these patients, the total number of levofloxacin-treated CAP patients with resistant *S. pneumoniae* increased to 18 with PRSP and 49 with PISP. The efficacy data that is analyzed in the Medical Officer's analyses is based upon the population of 18 PRSP and 49 PISP levofloxacin-treated CAP patients (Table 55).

> **MO Comment:** Fewer patients with PNSSP were identified among the comparator-treated patients (4 PRSP and 9 PISP cases). The lesser number of comparator cases reflects in part that 4 of the clinical studies were non-comparative (Table 55).

Table 55: Source of Patients with Community-Acquired Pneumonia due to Penicillin-Resistant *S. pneumoniae* (PRSP) or Penicillin-Intermediate *S. pneumoniae* (PISP)

Study No. (Location)	Design	Regimen (Duration)	Number of CAP Patients with PRSP	Number of CAP Patients with PISP
Original NDA Studies				
K90-071 (USA)	open label, randomized, comparative	Levo IV or PO vs Ceftriaxone IV or Cefuroxime PO +/- Erythromycin or Doxycycline (7-14 days)	1 (levo) 0 (cef)	4 (levo) 4 (cef)
M92-075 (USA)	open label, non-comparative	Levo IV or PO (7-14 days)	2 (levo)	3 (levo)
LOFBIV-MULT-001 (USA)	open label, non-comparative	Levo IV or PO (7-14 days)	1 (levo)	0 (levo)
Additional Studies				
LOFBIV-PCAP-001[a] (USA & Canada)	open label, non-comparative	Levo IV or PO (7-14 days)	5 (levo)	26 (levo)
CAPSS-018 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone and Erythromycin (IV) to Amoxicillin/Clav and Clarithromycin (7-14 days)	0 (levo) 3 (cef)	1 (levo) 4 (cef)
CAPSS-043 (USA)	open label, non-comparative (non-IND)	Levo IV or PO (7-14 days)	6 (levo)	14 (levo)
CAPSS-056 (USA)	open label, randomized, comparative (non-IND)	Levo IV or PO vs Ceftriaxone/ Azithromycin(PO) (10 days)	2 (levo) 1 (cef/az)	1 (levo) 1 (cef/az)
FF/93/355/02 (Europe, South Africa, Argentina)	double-blind, randomized, comparative	Levo PO vs Amox/Clav (7-10 days)	1 (levo) 0 (am/cl)	0 (levo) 0 (am/cl)
TOTALS			18 (levo) 4 (comp)	49 (levo) 9 (comp)

[a] Study initiated specifically to study resistant pneumococci in CAP

The CAP studies enrolled adult patients with clinical and radiographic evidence of CAP. Patients were excluded if they had received more than 24 hours of prior antimicrobial therapy for their current episode of CAP. Patients that had received 72 hours of therapy or more and were clinical failures were also permitted to enroll in some of the trials. Enrolled patients were to receive a total of 7 to 14 days of study treatment, which in the case of LEVAQUIN® was dosed as either 500 mg IV or PO daily. Following the completion of therapy, patients were assessed at either 1 or 2 post-therapy visits, with the first visit typically occurring 5 to 7 days post-therapy and the second visit (when included) 21 to 28 days post-therapy. (In some

studies, the protocol specified only one post-therapy assessment and that assessment could occur as early as 2 to 7 days post-therapy (CAPSS-056 and CAPSS-043)).

The Applicant's Post-Therapy response rates for levofloxacin for the composite data of patients with PRSP and PISP are shown in Table 54. The Applicant's Clinical Success and Microbiologic Eradication Rates for patients with CAP secondary to PRSP and PISP were 100%.

Medical Officer's Efficacy Analysis of LEVAQUIN® for the Treatment of CAP due to PRSP or PISP

The Medical Officer (MO) reviewed all of the PRSP and PISP CAP cases for both the levofloxacin and comparator-treated patients at the level of the case report forms.

One of the challenges in analyzing the data drawn from the 8 studies was dealing with the minor differences in study design and the timing of outcome assessments. The MO performed his own efficacy analysis in an attempt to achieve 2 main objectives. First, to standardize the time at which outcome assessments were made across studies. Second, to specify time windows post-therapy during which clinically meaningful and durable outcome assessment could be made. The composite data that are presented in this application were assembled from 8 separate studies in which the protocol specified timing and number of outcome assessments varied. In some of the studies, patients underwent only a single protocol-specified post-therapy evaluation and this evaluation could occur as early as 2 days post-therapy. Hence, patients evaluated on the 2nd day after completing therapy could have their final outcome assessments and complete the study. A final post-therapy assessment that occurs prior to allowing adequate time for (1) drug to clear from the system (based on the drug half-life) and (2) clinical manifestations of inadequately treated disease to recrudesce, could result in patients being classified as "cures" whose disease was merely suppressed or only partially treated.

The appropriate timing of outcome assessments is a recognized clinical trial design issue that has been discussed in CDER's most recent Draft Guidance document on developing antimicrobial drugs for the treatment of CAP. The Draft Guidance recommends that the test-of-cure visit should occur at least 7 days after the completion of therapy (assuming the study drugs have a short half-life). In the original NDA for LEVAQUIN®, the CAP studies were designed before this guidance was available and used a protocol specified window for the

Post-Therapy visit of 5 to 7 days followed by a Post-Study visit (21-28 days after completion of therapy) for some of the patients. Two of the ongoing non-IND studies that were initiated after the approval of LEVAQUIN® include a single Post-Therapy visit that could occur 2 to 7 days post-therapy (with no subsequent follow-up). Because of these differences and the concern that some of patients may be evaluated before allowing adequate time for study drug to clear and for manifestations of inadequately treated disease to recrudesce, the medical officer developed the following criteria defining "pivotal" and "supportive" cases. In order for a patient to be evaluable, a patient first had to meet the protocol specified evaluability criteria. Then in the MO efficacy analysis, cases were further divided into pivotal and supportive cases based on the timing of the test-of-cure visit(s). In order for a case to be considered a pivotal case, the following criteria had to be met:

- The test-of-cure visit must occur 5-21 days after the patient completed study drug in order for the patient to be a pivotal case.
- Patients' whose first post-therapy evaluation occurred 2 to 4 days after completing study drug and whose outcomes were cured or improved could remain in the pivotal case population if they underwent a subsequent evaluation that occurred on or after the 5th day after therapy was completed.
- Failure that occurred at any time after a patient had received at least 48 hours of study drug was to be considered within the pivotal group of cases

Supportive cases were those patients who underwent only a single post-therapy assessment that occurred between the 2nd and 4th day post-therapy. "Supportive" cases are defined as such because sufficient time has not elapsed between the end-of-therapy and the test-of-cure to allow time for drug to clear and for the manifestations of inadequately treated disease to dependably recrudesce in those patients that are inadequately treated. Hence, the nature of the data that supportive cases provide is not sufficient to independently substantiate the PRSP/PISP claim in CAP. Supportive cases can be used to complement the data provided by pivotal cases.

In the tables that follow, data is presented separately for those patients who provide "pivotal" data and for those who provide "supportive" data.

The MO efficacy analysis determined an "Overall Clinical Response" and "Overall Microbiological Response" instead of Post-Therapy and Post-Study outcomes. This approach is chosen in the MO Efficacy Analysis because of the variable timing and variable number of outcome assessments that were available across the 8 clinical studies. For those

patients that had 2 post-therapy visits, the results of both visits were considered in determining the "Overall Response."

The characteristics of the intent-to-treat, the pivotal, and the supportive patient populations for levofloxacin-treated patients with PRSP are summarized in Table 56. In the PRSP populations, over one-half of the patients were hospitalized, approximately one-third of the pneumonias were classified as severe or serious, and 45% of the pivotal cases were bacteremic.

Table 56: Patient Characteristics for Levofloxacin-Treated Patients with PRSP

Patient Characteristics	PRSP					
	Intent-to-Treat		Pivotal Cases		Supportive Cases	
	N = 18	(%)	N = 11	(%)	N = 4	(%)
Age						
Mean	54	-	46	-	55	-
Median	53	-	44	-	55	-
Range	24-96	-	24-74	-	42-67	-
Sex						
Male/Female	8/10	-	4/7	-	1/3	-
Race						
Caucasian/Black/Other	15/2/1	-	10/1/0	-	2/1/1	-
Bacteremia	6	(33)	5	(45)	1	(25)
Hospitalization						
Inpatient	11	(61)	7	(64)	2	(50)
Outpatient	6	(33)	4	(36)	1	(25)
Unkown	1	(6)	0	(0)	1	(25)
Pre-Study Antibiotics ≤ 24h Reported	4	(22)	3	(27)	1	(25)
Clinical Failure on Pre-Study Antibiotics	1	(6)	1	(9)	0	(0)
Severity						
Severe	5	(28)	5	(45)	0	(0)
Mild/Mod	4	(22)	4	(36)	0	(0)
Unknown	9	(50)	2	(18)	4	(100)
Pathogens Isolated						
S. pneumoniae only	15	(83)	9	(82)	4	(100)
S. pneumoniae + others	3	(17)	2	(18)	0	(0)

MO Comment: The subset of patients with CAP due to PRSP and bacteremia or disease classified as severe provide important information on the efficacy of levofloxacin in this subset of patients that would be expected to be more difficult to treat (i.e. in a group of patients in whom worse outcomes would be predicted).

One of the levofloxacin-treated patients (a pivotal case with PRSP) was judged to be a clinical failure on pre-study antimicrobial therapy and was subsequently enrolled in Study LOFBIV-PCAP-001. This patient (No. 1010) received azithromycin 500 mg on Study Day –3, azithromycin 250 mg on Study Day –2, and received no therapy on Study Day –1. On the following day (Study Day 1), the patient had continued clinical symptoms with fever to 101.8 °F and was judged a clinical failure. She was enrolled in Study LOFBIV-PCAP-001 and cultures of blood and a bronchial wash from admission (Study Day 1) grew PRSP. The erythromycin MIC against the organism was 8 mcg/mL (resistant). The patient was treated with levofloxacin 500 mg po QD for 14 days. She was assessed as a clinical cure and microbiological success at her Post-Therapy (day 6 post-therapy) and Post-Study (day 16 post-therapy) assessments.

The characteristics of the intent-to-treat, the pivotal, and the supportive patient populations for levofloxacin-treated patients with PISP are summarized in Table 57. Four of the 37 (11%) pivotal cases were bacteremic. Twenty-five of the 37 (68%) pivotal cases were inpatients at the time of study enrollment and 12 of 37 (32%) were classified as having severe pneumonia.

Table 57: Patient Characteristics for Levofloxacin-Treated Patients with PISP

Patient Characteristics	PISP					
	Intent-to-Treat		Pivotal Cases		Supportive Cases	
	N = 49	(%)	N = 37	(%)	N = 4	(%)
Age						
Mean	59	-	60	-	57	-
Median	62	-	63	-	62	-
Range	24-88	-	24-88	-	41-64	-
Sex						
Male/Female	28/21	-	24/13	-	1/3	-
Race						
Caucasian/Black/Other	35/12/2	-	26/10/1	-	3/1/0	-
Bacteremia	7	(14)	4	(11)	2	(50)
Hospitalization						
Inpatient	33	(67)	25	(68)	3	(75)
Outpatient	15	(31)	12	(32)	0	(0)
Unknown	1	(2)	0	(0)	1	(25)
Pre-Study Antibiotics ≤ 24h Reported	10	(20)	9	(24)	1	(25)
Clinical Failure on Pre-Study Antibiotics	5	(10)	5	(14)	0	(75)
Severity						
Severe	14	(29)	12	(32)	0	(0)
Mild/Mod	19	(39)	18	(49)	0	(0)
Unknown	16	(33)	7	(19)	4	(100)
Pathogens Isolated						
S. pneumoniae only	33	(67)	24	(65)	4	(100)
S. pneumoniae + others	16	(33)	13	(35)	0	(0)

Five patients with PISP were enrolled after being declared clinical failures following therapy with other antimicrobial agents. Of these 5 patients, all 5 had PISP grown from a respiratory culture from the day of admission to study. One of the 5 also had PISP cultured from blood. Two patients received 3 days of therapy before enrollment, the other 3 patients received 4, 7, and 9 days of prior antimicrobial therapy. After treatment with study drug, all 5 patients were assessed as clinical successes and microbiological eradications.

Of the 18 patients identified with PRSP, 3 were non-evaluable. Of the remaining 15 patients (11 pivotal and 4 supportive cases), all were scored as overall clinical successes and microbiological eradications (Table 58). The exact 95% confidence interval (CI) about 15 of 15 (100%) cases is (78.2%, 100%). For 11 out of 11 (100%) pivotal cases, the exact 95% CI is (71.5%, 100%).

Table 58: MO's Efficacy Analysis of Overall Clinical and Microbiological Outcomes for Levofloxacin-Treated Patients with PRSP or PISP

Penicillin Susceptibility Pivotal or Supportive Case Clinical Outcome	Levofloxacin-Treated Patients			
	Overall Clinical Response		**Overall Microbiological Response**	
PRSP	N = 18	(%)	N = 18	(%)
Pivotal Cases				
Pivotal Success[a]	11/11	(100)	11/11	(100)
Failure	0/11	(0)	0/11	(0)
Supportive Cases				
Supportive Success[a]	4/4	(100)	4/4	(100)
Non-evaluable	3		3	
PISP	N = 49	(%)	N = 49	(%)
Pivotal Cases				
Pivotal Success[a]	37/37	(100)	37/37	(100)
Failure	0/37	(0)	0/37	(0)
Supportive Cases				
Supportive Success[a]	4/4	(100)	4/4	(100)
Non-evaluable	8		8	

[a]Note: Success includes both cure and improvement for Clinical Response and includes eradication and presumed eradication for Microbiological Response.
[b] In this population, all patients with a clinical response score of "improved" at the first post-therapy assessment had a subsequent post-therapy assessment at which they achieved "cure."

The reasons that the 3 PRSP patients were considered non-evaluable are as follows:

- Pt. No. 1412, Study CAPSS-043
  - ticarcillin-clavulanate was added on Study Day 2 (prior to 48 hours of levofloxacin therapy) and was discontinued on Study Day 3
  - the patient's test-of-cure assessment occurred on Study Day 12 while the patient was on levofloxacin therapy (levofloxacin given Days 1 through 14)
- Pt. No. 17902 Study CAPSS-043
  - the patient's test-of-cure assessment occurred on Study Day 7 while the patient was on levofloxacin therapy (levofloxacin given Days 1 through 14)
  - admission CXR showed "no pneumonia" and repeat CXR obtained on Day 7 (day of the patient's test-of-cure) showed pneumonia
- Pt. No. 24826 Study CAPSS-043
  - the patient's test-of-cure assessment occurred on Study Day 16 while the patient was on levofloxacin therapy (levofloxacin given Days 1 through 20)

MO Comment: Review of the CRFs for Patient 1412, Study CAPSS-043, do not provide a reason for why ticarcillin-clavulanate was added on Study Day 2 (prior to 48 hours of levofloxacin therapy). Similarly there is no reason provided for why ticarcillin-clavulanate was discontinued on Study Day 3. This brief addition of ticarcillin-

clavulanate prior to 48 hours of levofloxacin therapy appears to represent the individual physician's preference.

MO Comment: Review of the CRFs for Patient 17902, Study CAPSS-043 reveals that the patient was scored as a clinical cure at the test-of-cure visit on Study Day 7.

MO Comment: Patient 24826, Study CAPSS-043 was scored as a clinical cure at his test-of-cure assessment on Study Day 16.

The reasons that the 8 levofloxacin-treated PISP patients were considered non-evaluable are as follows:

- Pt. No. 1703 Study K90-071
  - patient received other than the specified dose of study drug (levofloxacin 488 mg po BID)
- Pt. No. 1029 Study LOFBIV-PCAP-001
  - patient received non-protocol antimicrobial therapy between the Post-Therapy and the Post-Study assessment (aerosolized gentamicin for pseudomonas bronchitis)
- Pt. No. 28051, Study LOFBIV-PCAP-001
  - patient received non-protocol antimicrobial therapy upon arrival at her nursing home "per nursing home standard procedures" for a resolving radiographic infiltrate in the absence of clinical symptoms of pneumonia
- Pt. No. 3604, Pt. No. 5305, Pt. No. 6501 Study CAPSS-043
  - patient's test-of-cure evaluation occurred on post-therapy day 1
- Pt. No. 16230, and Pt. No. 16279 Study CAPSS-043
  - non-evaluable because of inappropriate microbiological evaluation

The 4 PRSP cases that were considered supportive successes had their final outcome assessments between the 2nd and 4th days post-therapy. These 4 patients are described below:

- Pt. No. 8902, Study CAPSS-043
  50-year-old male with COPD and clinical and radiographic evidence of pneumonia. Upon admission, PRSP was cultured from sputum and a blood culture was negative. He was hospitalized and treated with levofloxacin Study Days 1 through 14. His test-of-cure assessment was performed on Study Day 17 (3rd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.
- Pt. No. 508, Study CAPSS-056
  67-year-old female with clinical and radiographic evidence of pneumonia. Upon admission, PRSP was cultured from sputum and a blood culture was negative. She was hospitalized and treated with levofloxacin Study Days 1 through 10. Her test-of-cure assessment was performed on Study Day 13 (3rd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.

- Pt. No. 29111, Study CAPSS-043
  42-year-old female with clinical and radiographic evidence of pneumonia. Upon admission, PRSP was cultured from sputum. She was treated as an outpatient with levofloxacin Study Days 1 through 10. Her test-of-cure assessment was performed on Study Day 13 (3rd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.
- Pt. No. 2221, Study CAPSS-056
  60-year-old female with a "mechanical" cardiac valve with clinical and radiographic evidence of pneumonia. Upon admission, PRSP was cultured from sputum and blood. She was treated with levofloxacin Study Days 1 through 14. Her test-of-cure assessment was performed on Study Day 16 (2nd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.

The 4 PISP cases that were considered supportive successes had their final outcome assessments between the 2nd and 4th days post-therapy. These four patients are described below:

- Pt. No. 3105, Study CAPSS-043
  61-year-old female with clinical and radiographic evidence of pneumonia. Upon admission, PISP was cultured from sputum and a blood culture was negative. She was an inpatient when therapy was initiated. She was treated with levofloxacin Study Days 1 to 14. Her test-of-cure assessment was performed on Study Day 16 (2nd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.
- Pt. No. 14901, Study CAPSS-043
  41-year-old female with clinical and radiographic evidence of pneumonia. Upon admission, PISP was cultured from sputum and blood. She was an inpatient when therapy was initiated. She was treated with levofloxacin Study Days 1 to 14. Her test-of-cure assessment was performed on Study Day 17 (3rd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.
- Pt. No. 20103, Study CAPSS-043
  64-year-old female with clinical and radiographic evidence of pneumonia. Upon admission, PISP was cultured from blood and a sputum culture was negative. She was an inpatient when therapy was initiated. She was treated with levofloxacin Study Days 1 to 14. Her test-of-cure assessment was performed on Study Day 16 (2nd day post-therapy) at which time the assessment was clinically improved and microbiologic eradication.
- Pt. No. 2216, Study CAPSS-056
  62-year-old male with clinical and radiographic evidence of pneumonia. Upon admission, PISP was cultured from sputum and a blood culture was negative. He was treated with levofloxacin Study Days 1 to 10. His test-of-cure assessment was performed on Study Day 12 (2nd day post-therapy) at which time the assessment was clinical cure and microbiologic eradication.

One death occurred amongst the levofloxacin-treated patients with PRSP or PISP, Pt. No. 55001 from Study LOFBIV-PCAP-001. The patient was a 68-year-old female with steroid-dependent asthma who was admitted with clinical and radiographic evidence of pneumonia. She was treated with levofloxacin 500 mg QD for a total of 16 days. On the 5th day post-therapy she was assessed as a clinical cure and microbiological eradication based on clinical and radiographic improvement. Arrangements were being made to discharge the patient from the hospital prior to her Post-Study visit (scheduled for Days 21-28). However, while in the hospital, the patient experienced an episode of severe bronchospasm. Arrangements for transfer to the ICU were initiated. However, the patient died before the transfer to the ICU could be accomplished. The patient's cause of death was ascribed to severe bronchospasm related to her underlying steroid-dependent asthma.

The clinical and microbiological response rates stratified by investigator are displayed in Table 59. Response rates are presented for the pivotal cases and the supportive cases by degree of penicillin resistance. The majority of the pivotal PRSP and a considerable proportion of the pivotal PISP cases were from one center.

Table 59: Clinical and Microbiological Response Rates by Investigator for PRSP and PISP Cases for Levofloxacin-Treated Patients

Investigator	Degree of Penicillin-Resistance and Type of Case			
	PRSP		PISP	
	Pivotal	Supportive	Pivotal	Supportive
	# Successes/ # Patients	# Successes/ # Patients	# Successes/ # Patients	# Successes/ # Patients
	---	---	1/1	---
	---	1/1	---	---
	---	---	1/1	---
	---	---	5/5	---
	1/1	0/0	---	---
	---	---	1/1	---
	6/6	0/0	11/11	---
	---	1/1	---	---
	1/1	0/0	---	---
	---	---	2/2	---
	1/1	0/0	4/4	---
	1/1	0/0	---	---
	---	---	1/1	---
	---	1/1	1/1	2/2
	---	---	---	1/1
	---	---	1/1	---
	---	---	3/3	---
	---	---	1/1	---
	---	---	1/1	---
	1/1	0/0	---	---
	---	---	1/1	---
	---	---	1/1	---
	---	---	1/1	---
	0/0	1/1	---	---
	---	---	1/1	---
	---	---	---	1/1
	11/11	4/4	37/37	4/4

Similar data on patient characteristics and efficacy results are presented for the limited number of patients who received comparator treatment who had either PRSP or PISP. The data are presented separately because they are drawn from only a subset of studies from which the data for levofloxacin-treated patients are derived. Although the data from comparator patients are not directly comparable with the composite data from the

levofloxacin-treated patients, the data do give an impression of the patient's characteristics and outcomes in the limited number of comparator-treated patients with PRSP and PISP.

The demographic and baseline characteristics of the comparator-treated patients with PRSP or PISP are presented in Table 60. In the comparator-treated patients with PRSP, all of the patients were bacteremic and all of the evaluable patients were hospitalized with disease classified as severe.

Table 60: Patient Characteristics for Comparator[1]-Treated Patients by Level of Penicillin-Resistance and Population

Patient Characteristics	PRSP				PISP			
	Intent-to-Treat		Pivotal Cases		Intent-to-Treat		Pivotal Cases	
	N = 4	(%)	N = 3	(%)	N = 9	(%)	N =4	(%)
Age								
Mean	55	-	59	-	50	-	45	-
Median	53	-	55	-	49	-	45	-
Range	43-71	-	50-71	-	26-75	-	26-65	-
Sex								
Male/Female	2/2	-	2/1	-	6/3	-	3/1	-
Race								
Caucasian/Black/Other	2/2/0	-	1/2/0	-	6/3/0	-	3/1/0	-
Bacteremia	4	(100)	3	(100)	5	(56)	1	(40)
Hospitalization								
Inpatient	3	(75)	3	(100)	6	(67)	2	(50)
Outpatient	0	(0)	0	(0)	2	(22)	2	(50)
Unknown	1	(25)	0	(0)	1	(11)	0	(0)
Pre-Study Antibiotics ≤ 24h Reported	1	(25)	1	(33)	4	(44)	0	(0)
Pre-Study Antibiotics ≥ 72h	0	(0)	0	(0)	0	(0)	0	(0)
Severity								
Severe or Serious	3	(75)	3	(100)	5	(56)	1	(20)
Mild/Mod	0	(0)	0	(0)	3	(33)	3	(60)
Unknown	1	(25)	0	(0)	1	(11)	0	(20)
Pathogens Isolated								
S. pneumoniae only	4	(100)	3	(100)	6	(67)	2	(50)
S. pneumoniae + others	0	(0)	0	(0)	3	(33)	2	(50)

[1] Note: Only 4 of the 8 studies were comparative studies. For a summary of the comparator regimens and study designs see Table 55.
Note: There were no "supportive" cases in the comparator arms

In the small number of comparator-treated cases with PRSP, all 3 of the 3 evaluable cases were considered pivotal clinical and microbiological successes (Table 61).

Table 61: MO's Efficacy Analysis of Overall Clinical and Microbiological Outcome for Comparator-Treated Patients with PRSP or PISP

Penicillin Susceptibility Pivotal or Supportive Case Clinical Outcome	Comparator[c] – Treated Patients			
	Clinical Response		**Microbiological Response**	
PRSP	N = 4	(%)	N = 4	(%)
Pivotal Cases				
Pivotal Success[a]	3/3	(100)	3/3	(100)
Failure	0/3	(0)	0/3	(0)
Supportive Cases				
Supportive Success[a, b]	-	-	-	-
Non-evaluable	1		1	
PISP	N = 9	(%)	N = 9	(%)
Pivotal Cases				
Pivotal Success[a]	4/4	(100)	4/4	(100)
Failure	0/4	(0)	0/4	(0)
Supportive Cases				
Supportive Success[a, b]	-	-	-	-
Non-evaluable	5		5	

[a] Note: Success includes both cure and improvement. In this population all patients scored as improved achieved cure at their final assessment
[b] There were no supportive Comparator PRSP or PISP cases
[c] Note: Only 4 of the 8 studies were comparative studies. For a summary of the comparator regimens and study designs see Table 55.

The reason that one patient with PRSP was considered non-evaluable is as follows:

- Pt. No. 1304, Study CAPSS-056, had PRSP isolated from blood and sputum. The patient received 6 days of study treatment with ceftriaxone (Days 1 to 3) and azithromycin (Days 1 to 6), per protocol. The patient was withdrawn from the study on Day 6 when the sensitivities of the patient's *S. pneumoniae* isolate returned showing resistance to azithromycin (MIC>8 mcg/mL) and ceftriaxone (MIC= 2 mcg/mL). The patient was scored as improved at the time of study withdrawal. The records do not mention if the patient was then placed on other antimicrobial therapy.

Five patients with PISP were non-evaluable. The reasons for their non-evaluability were

- Pt. No. 7005, CAPSS-018
  patient died prior to receiving 48 hours of study therapy (more details below)
- Pt. No. 217, K90-071
  patient received other than the protocol specified dose of study drug
- Pt. No. 9007, CAPSS-018
  Patient taken off of study drug (changed to alternative antibiotics) prior to receiving 48-hours of study therapy

- Pt. No. 2223, CAPSS-056
  patient received an antibiotic (grepafloxacin) for an alternative condition ("thrombosis of right brachiocephalic vein") on the day of the post-therapy assessment
- Pt. No. 5004, CAPSS-018
  Study drug discontinued prior to the 5th day of therapy (in a patient otherwise clinically improving) because of urticaria possibly related to study drug

The only death amongst the comparator treated patients is patient number 7005 from CAPSS-018. This 49-year-old male had a medical history of chronic alcohol abuse, hepatitis C infection, cirrhosis, pancytopenia, hypertension, and congestive heart failure. He was admitted with clinical and radiographic signs of pneumonia and altered mental status. He was treated with ceftriaxone 2 g IV q24h and erythromycin 500 mg IV q6h. PISP sensitive to ceftriaxone (MIC of 0.25 mcg/mL) and erythromycin (MIC of 0.03 mcg/mL) grew from his admission blood culture. The patient required levophed and dopamine support on Study Day 1. He also required mechanical ventilation. He expired on Study Day 2 secondary to septic shock.

The clinical and microbiological success rates by investigator were analyzed for the comparator-treated patients with CAP secondary to PRSP and PISP (Table 62). The small number of comparator-treated patients with PRSP or PISP are distributed across an equally small number of study centers. Only one study center enrolled more than one comparator-treated patient with PRSP.

Table 62: Overall Clinical and Microbiological Response Rates by Investigator for PRSP and PISP Cases for Comparator[1]-Treated Patients

Investigator	Degree of Penicillin-Resistance and Type of Case			
	PRSP		PISP	
	Pivotal	Supportive	Pivotal	Supportive
	#Successes/ #Patients	#Successes/ #Patients	#Successes/ #Patients	#Successes/ #Patients
	---	---	1/1	---
	2/2	---	1/1	---
	---	---	1/1	---
	1/1	---	---	---
	---	---	1/1	---
Total	3/3	---	4/4	---

[1] Note: Only 4 of the 8 studies were comparative studies. For a summary of the comparator regimens and study designs see Table 55..

Summary of the Efficacy Results for Levofloxacin for the Treatment of Community-Acquired Pneumonia due to PRSP

In the clinical studies of CAP submitted in the original NDA, levofloxacin achieved clinical success rates between 93% and 95% and microbiologic eradication rates within the range of 94% to 96%. In the one CAP trial with a comparator arm, the comparator regimen achieved a clinical success rate of 83% and a microbiologic eradication rate of 81%. Clinical success rates from these trials for levofloxacin-treated patients with *S. pneumoniae* isolated from a culture obtained at admission were approximately 95% for levofloxacin and 84% for the comparator regimen (only one of the 2 major studies from the original NDA had a comparator arm).

The data that are presented in support of the current supplemental NDA were collected from 8 clinical trials of levofloxacin for CAP. A total of 18 PRSP and 49 PISP isolates from levofloxacin-treated patients were identified. Of the 18 cases of PRSP, 11 of 11 (100%) were considered to be pivotal clinical and microbiologic successes, 4 of 4 (100%) were supportive clinical and microbiological successes, and the remaining 3 cases were non-evaluable. Of the 49 cases of PISP, 37 of 37 (100%) were considered pivotal clinical successes, 4 of 4 were considered supportive clinical and microbiological successes, and 8 were non-evaluable. A total of 4 PRSP and 9 PISP isolates from comparator-treated patients were identified. Of the 4 cases of PRSP, 3 of 3 (100%) were considered to be pivotal clinical and microbiologic successes, and the remaining case was non-evaluable. Of the 9 cases of CAP due to PISP, 4 of 4 (100%) were considered pivotal clinical successes, and 5 were non-evaluable (Table 63).

In the group of evaluable pivotal and supportive cases of levofloxacin-treated patients with CAP due to PRSP (n=15), there were 6 bacteremic patients and 5 patients with disease classified as severe. All achieved clinical success and microbiological eradication. In the 3 evaluable patients treated with comparator therapy, all 3 were bacteremic and had disease classified as severe. All 3 of these comparator-treated patients achieved clinical success and microbiological eradication.

Table 63: Summary Table of Clinical and Microbiological Response Rates[a] for PRSP and PISP

Penicillin Susceptibility for *S. pneumonia* *Study Population* Pivotal or Supportive Cases	Study Therapy					
	Levofloxacin 500 mg QD			Comparator Regimens		
		Success			Success	
	N	n	(%)	N	n	(%)
PRSP[b]						
Combined Comparative Studies[c]						
Pivotal Success	2	2	100	3	3	100
Supportive Success	2	2	100	0	--	--
Non-Evaluable	0	--	--	1	--	--
Combined Non-Comparative Studies[d]						
Pivotal Success	9	9	100	--	--	--
Supportive Success	2	2	100	--	--	--
Non-Evaluable	3	--	--	--	--	--
Total	**18**			**4**		
PISP[b]						
Combined Comparative Studies[c]						
Pivotal Success	4	4	100	4	4	100
Supportive Success	1	1	100	0	--	--
Non-Evaluable	1	--	--	5	--	--
Combined Non-Comparative Studies[d]						
Pivotal Success	33	33	100	--	--	--
Supportive Success	3	3	100	--	--	--
Non-Evaluable	7	--	--	--	--	--
Total	**49**			**9**		

[a] clinical and microbiological response rates were numerically the same. Clinical success = cure or improved; "Microbiological success" = eradication or presumed eradication

[b] PRSP, MIC ≥2.0 µg/mL; PISP, MIC 0.1-1.0 µg/mL

[c] the comparative clinical studies include K90-071, CAPSS-018, CAPSS-056, FF/95/355/02

[d] the non-comparative clinical studies include M92-075, LOFBIV-MULT-001, LOFBIV-PCAP-001, CAPSS-043

Overall, the proportion of patients with CAP and PRSP or PISP achieving successful outcomes was comparable with what was observed for levofloxacin for the treatment of CAP (of all causes) and CAP secondary to *Streptococcus pneumoniae* in the original NDA clinical studies and in Study LOFBIV-PCAP-001.

MEDICAL OFFICER'S FINAL RECOMMENDATIONS

The MO finds that the information presented in the NDA 20-634 SE-008 and NDA 20-635 SE-007 provides substantial evidence of activity for levofloxacin in the treatment of CAP due to PRSP. The MO's recommendation for approval of the aforementioned efficacy supplement is based primarily upon the data presented for the following 8 components

1. The efficacy profile and the quantity and quality of data on levofloxacin for the treatment of CAP
2. The efficacy profile and the quality and quantity of data on levofloxacin for the treatment of CAP due to *Streptococcus pneumoniae*
3. The efficacy profile and the quality and quantity of data for levofloxacin for the treatment of CAP in the subset of patients identified with CAP due to PRSP or PISP
4. The efficacy profile and the quality and quantity of data for levofloxacin for the treatment of CAP in the subset of patients identified with bacteremia due to PRSP or PISP
5. The efficacy profile and the quality and quantity of data for levofloxacin for the treatment of CAP due to PRSP and PRSP in the subset of patients identified with disease classified as severe
6. That the efficacy data that are presented represents the entire experience of RWJPRI, its affiliate Ortho McNeil Pharamceutical Inc., and its partners Aventis (formerly Hoescht Marion Roussel) and Daiichi Pharmaceuticals, with levofloxacin in efficacy studies for the treatment of CAP due to PRSP or PISP at the US approved dosage.
7. That the mechanism of levofloxacin resistance is mechanistically separate from the mechanism for penicillin resistance
8. That the current levels of penicillin and levofloxacin cross-resistance is currently low

MO Comment: The final component above (number 8) would be expected to change with time based upon information presented at the Anti-Infective Drug Product Advisory Committee. Therefore, [redacted]

MEDICAL OFFICER'S RECOMMENDED CHANGES TO THE LEVAQUIN® PRODUCT LABEL

MO Comment: The portions of the LEVAQUIN® product label in which the MO recommends changes to the product label are excerpted below. The Applicant's proposed changes are shaded. The Applicant's changes that are rejected by the MO have a single line strike through. The MO's recommended changes to the label are shaded and are also double underlined.

MO Recommendation: In the **MICROBIOLOGY** subsection, the MO recommends that the phrase "including penicillin-resistant strains" be further defined in a Note in the **MICROBIOLOGY** subsection as those strains of *S. pneumoniae* with an MIC ≥ 2 µg/mL. The proposed addition to the Applicant's original proposal is shown in the excerpted portion of the label below. Note: The change involving *Pantoea (Enterobacter) agglomerans* is a change from the Agency's Microbiology Reviewer and is included in order to maintain consistency.

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 aminoglycosides, 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)
Staphlyococcus saprophyticus

Streptococcus pneumoniae (including penicillin-resistant strains*)
Streptococcus pyogenes

*Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC ≥ 2 µg/mL

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 in 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 values) 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 lwoffii
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes

Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Pantoea (Enterobacter) agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens

Serratia marcescens

Anaerobic gram-positive microorganisms
Clostridium perfringens

MO Recommendation: Under the **Community-acquired pneumonia** indication, the MO recommends that the MIC to penicillin that denotes penicillin-resistant *S. pneumoniae* be included. The suggested change to the proposed labeling is shown below.

INDICATIONS AND USAGE

LEVAQUIN Tablets are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. _

LEVAQUIN Injection is indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below, when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute maxillary sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial exacerbation of chronic bronchitis due to *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

Community-acquired pneumonia due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains, MIC for penicillin ≥ 2 µg/mL), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES.**)

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus*, or *Streptococcus pyogenes*.

MO Recommendations: The MO recommends the following changes to the Applicant's proposed addition to the **CLINICAL STUDIES** section:

1. The proposed addition to the **CLINICAL STUDIES** section should include information on the responses in comparator arms of the studies where comparator information is available. The absence of comparator information in the Applicant's proposed labeling makes the numerical rates presented less informative.

2. The proposed addition to the **CLINICAL STUDIES** section should also include information on the number of patients identified with CAP due to PRSP and the number of the these patients that were evaluable.
3. The MO's suggested changes are incorporated in a text format rather than a table. The recommended changes are shown in the excerpted portion of the proposed label below.

CLINICAL STUDIES

Community-Acquired Bacterial Pneumonia
Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%) [95% CI of -19,-6]. In the second study, 264 patients were enrolled in a prospective, multi-center, noncomparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies were as follows:

Pathogen	No. Pathogens	Microbiologic Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Additional studies were initiated to evaluate the utility of LEVAQUIN in community-acquired pneumonia due *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC for penicillin≥2 µg/mL). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double blind study, two open labeled randomized studies, [redacted]; and three open label non-comparative studies. The total number of clinically evaluable patients with *S.pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with *S. pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator-treated patients with *S. pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* strains (MIC for penicillin≥2 µg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having

severe disease. Of the 4 comparator-treated patients with community-acquired pneumonia due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator-treated patients achieved clinical success. All three of the comparator-treated patients were bacteremic and had disease classified as severe.

MO Comment/Recommendation: The MO recommends the addition of a Patient Information Leaflet at the end of the product label. The Patient Information Leaflet should provide information to be used by patients that will enhance the safe and appropriate use of levofloxacin. The recommended Patient Information Leaflet is based largely upon the other recent Patient Information Leaflets that have been included as part of the product labeling for other recently approved quinolones (moxifloxacin and gatifloxacin). The proposed Patient Information Leaflet follows:

Patient Information About:

LEVAQUIN®

(levofloxacin tablets)
250 mg Tablets and 500 mg Tablets

This leaflet contains important information about LEVAQUIN® (levofloxacin), and should be read completely before you begin treatment. This leaflet does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This leaflet does not list all benefits and risks of LEVAQUIN®. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about LEVAQUIN® talk to your health care professional. Only your health care professional can determine if LEVAQUIN® is right for you.

What is LEVAQUIN®?

LEVAQUIN® is a quinolone antibiotic used to treat lung, sinus, skin, and urinary tract infections caused by certain germs called bacteria. LEVAQUIN® kills many of the types of bacteria that can infect the lungs, sinuses, skin, and urinary tract and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.

Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). LEVAQUIN®, like other antibiotics, does not kill viruses.

You should contact your doctor if you think that your condition is not improving while taking LEVAQUIN®. LEVAQUIN® Tablets are either terra cotta pink for the 250 mg tablet or peach colored for the 500 mg tablet.

How and when should I take LEVAQUIN®?

LEVAQUIN® should be taken once a day for 3, 7, 10, or 14 days depending on your prescription. It should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day.

You may begin to feel better quickly; however, in order to make sure that all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of LEVAQUIN® even if you missed a dose by mistake. You should not take a double dose.

Who should not take LEVAQUIN®?

You should not take LEVAQUIN® if you have ever had a severe allergic reaction to any of the group of antibiotics known as "quinolones" such as ~~[redacted]~~ or ciprofloxacin.

If you are pregnant or are planning to become pregnant while taking LEVAQUIN®, talk to your doctor before taking this medication. LEVAQUIN® is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.

LEVAQUIN® is not recommended for children.

What are the possible side effects of LEVAQUIN®?

LEVAQUIN® is generally well tolerated. The most common side effects caused by LEVAQUIN®, which are usually mild, include nausea, diarrhea, itching, abdominal pain, dizziness, flatulence, rash, and vaginitis in women.

You should be careful about driving or operating machinery until you are sure LEVAQUIN® is not causing dizziness.

~~[redacted]~~ even after just one dose. If you develop hives, skin rash, or other symptoms of an allergic reaction, you should stop taking this medicine and call your doctor.

Some quinolone antibiotics have been associated with the development of phototoxicity ("sunburns" and "blistering sunburns") following exposure to sunlight or other sources of ultraviolet light such as artificial ultraviolet light used in tanning salons. LEVAQUIN® has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking LEVAQUIN®.

If you have diabetes and you develop a hypoglycemic reaction while on LEVAQUIN®, you should stop taking LEVAQUIN® and call your health care professional.

Convulsions have been infrequently reported in patients receiving quinolone antibiotics including LEVAQUIN®. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.

If you notice any side-effects not mentioned in this leaflet or you have concerns about the side effects you are experiencing, please inform your health care professional.

What about other medicines I am taking?

Taking warfarin (Coumadin®) and LEVAQUIN® together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your doctor.

Many antacids and multivitamins may interfere with the absorption of LEVAQUIN® and may prevent it from working properly. You should take LEVAQUIN® either 2 hours before or 2 hours after taking these products.

It is important to let your health care provider know all of the medicines you are using.

Other information

Take your dose of LEVAQUIN® once a day.

Complete the course of medication even if you are feeling better.

Keep this medication out of the reach of children.

This information does not take the place of discussions with your doctor or health care professional about your medical condition or your treatment.

References

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DFS Keywords
Admin: review
Study type: study clin uncontrolled
Drug class: class quinolone
Indication: indic resistance PRSP; indic pneumonia, CAP
Special populations: pop adult