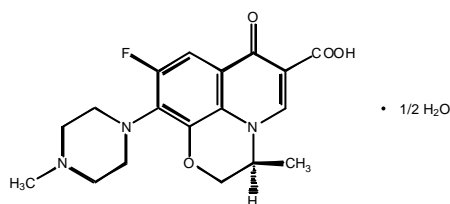


1 **LEVAQUIN[®] Tablets/Injection**
2 **(levofloxacin tablets/injection)**

3
4 **DESCRIPTION**

5 LEVAQUIN[®] (levofloxacin tablets/injection) Tablets/Injection are synthetic
6 broad spectrum antibacterial agents for oral and intravenous administration.
7 Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure
8 (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical
9 name is (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-
10 7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

11
12 The chemical structure is:



14 Its empirical formula is C₁₈H₂₀FN₃O₄ • ½ H₂O and its molecular weight is
15 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or
16 crystalline powder. The molecule exists as a zwitterion at the pH conditions in
17 the small intestine.

18
19 The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin is
20 essentially constant (approximately 100 mg/mL). Levofloxacin is considered
21 *soluble to freely soluble* in this pH range, as defined by USP nomenclature.
22 Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7
23 (272 mg/mL) and is considered *freely soluble* in this range. Above pH 6.7, the
24 solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of
25 approximately 6.9.

26
27 Levofloxacin has the potential to form stable coordination compounds with
28 many metal ions. This in vitro chelation potential has the following formation
29 order: Al⁺³>Cu⁺²>Zn⁺²>Mg⁺²>Ca⁺².

30
31 LEVAQUIN Tablets are available as film-coated tablets and contain the
32 following inactive ingredients:

33
34 250 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose,
35 crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene
36 glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.

37
38 500 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose,
39 crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene

40 glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron
41 oxides.

42

43 750 mg (as expressed in the anhydrous form): hydroxypropyl methylcellulose,
44 crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene
45 glycol, titanium dioxide, polysorbate 80.

46

47 LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free aqueous
48 solution of levofloxacin with pH ranging from 3.8 to 5.8. LEVAQUIN Injection in
49 Premix Flexible Containers is a sterile, preservative-free aqueous solution of
50 levofloxacin with pH ranging from 3.8 to 5.8. The appearance of LEVAQUIN
51 Injection may range from a clear yellow to a greenish-yellow solution. This does
52 not adversely affect product potency.

53

54 LEVAQUIN Injection in Single-Use Vials contains levofloxacin in Water for
55 Injection. LEVAQUIN Injection in Premix Flexible Containers is a dilute,
56 non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in
57 5% Dextrose (D₅W). Solutions of hydrochloric acid and sodium hydroxide may
58 have been added to adjust the pH.

59

60 The flexible container is fabricated from a specially formulated non-plasticized,
61 thermoplastic copolyester (CR3). The amount of water that can permeate from
62 the container into the overwrap is insufficient to affect the solution significantly.
63 Solutions in contact with the flexible container can leach out certain of the
64 container's chemical components in very small amounts within the expiration
65 period. The suitability of the container material has been confirmed by tests in
66 animals according to USP biological tests for plastic containers.

67

68 **CLINICAL PHARMACOLOGY**

69 The mean \pm SD pharmacokinetic parameters of levofloxacin determined under
70 single and steady state conditions following oral (p.o.) or intravenous (i.v.)
71 doses of levofloxacin are summarized in Table 1.

72

73 **Absorption**

74 Levofloxacin is rapidly and essentially completely absorbed after oral
75 administration. Peak plasma concentrations are usually attained one to two
76 hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a
77 750 mg tablet of levofloxacin are both approximately 99%, demonstrating
78 complete oral absorption of levofloxacin. Following a single intravenous dose of
79 levofloxacin to healthy volunteers, the mean \pm SD peak plasma concentration
80 attained was 6.2 \pm 1.0 μ g/mL after a 500 mg dose infused over 60 minutes and
81 11.5 \pm 4.0 μ g/mL after a 750 mg dose infused over 90 minutes.

82

83 Levofloxacin pharmacokinetics are linear and predictable after single and
84 multiple oral /or i.v. dosing regimens. Steady-state conditions are reached
85 within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The
86 mean \pm SD peak and trough plasma concentrations attained following multiple
87 once-daily oral dosage regimens were approximately 5.7 \pm 1.4 and 0.5 \pm 0.2

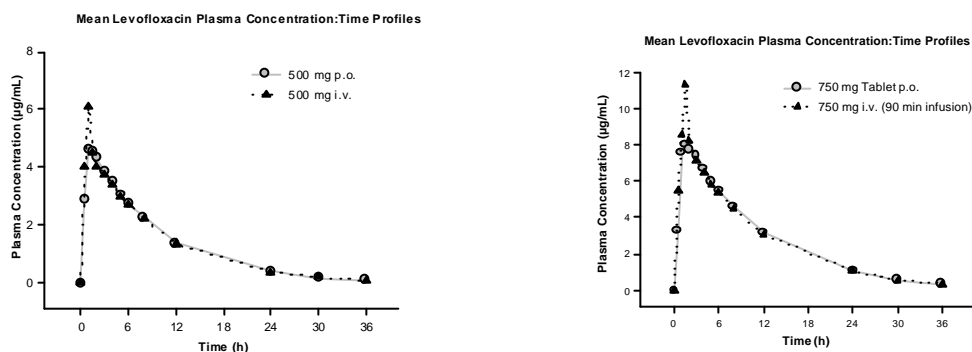
88 $\mu\text{g/mL}$ after the 500 mg doses, and 8.6 ± 1.9 and $1.1 \pm 0.4 \mu\text{g/mL}$ after the
89 750 mg doses, respectively. The mean \pm SD peak and trough plasma
90 concentrations attained following multiple once-daily i.v. regimens were
91 approximately 6.4 ± 0.8 and $0.6 \pm 0.2 \mu\text{g/mL}$ after the 500 mg doses, and 12.1
92 ± 4.1 and $1.3 \pm 0.71 \mu\text{g/mL}$ after the 750 mg doses, respectively.

93

94 Oral administration of a 500-mg LEVAQUIN tablet with food slightly prolongs
95 the time to peak concentration by approximately 1 hour and slightly decreases
96 the peak concentration by approximately 14%. Therefore, levofloxacin tablets
97 can be administered without regard to food.

98

99 The plasma concentration profile of levofloxacin after i.v. administration is
100 similar and comparable in extent of exposure (AUC) to that observed for
101 levofloxacin tablets when equal doses (mg/mg) are administered. Therefore,
102 the oral and i.v. routes of administration can be considered interchangeable.
103 (See following chart.)



104
105

106 Distribution

107 The mean volume of distribution of levofloxacin generally ranges from 74 to
108 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread
109 distribution into body tissues. Levofloxacin reaches its peak levels in skin
110 tissues and in blister fluid of healthy subjects at approximately 3 hours after
111 dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the
112 blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily
113 oral administration of 750 mg and 500 mg levofloxacin, respectively, to healthy
114 subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue
115 concentrations were generally 2- to 5- fold higher than plasma concentrations
116 and ranged from approximately 2.4 to 11.3 $\mu\text{g/g}$ over a 24-hour period after a
117 single 500 mg oral dose.

118

119 In vitro, over a clinically relevant range (1 to 10 $\mu\text{g/mL}$) of serum/plasma
120 levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to
121 serum proteins across all species studied, as determined by the equilibrium
122 dialysis method. Levofloxacin is mainly bound to serum albumin in humans.
123 Levofloxacin binding to serum proteins is independent of the drug
124 concentration.

125

126 **Metabolism**

127 Levofloxacin is stereochemically stable in plasma and urine and does not invert
128 metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited
129 metabolism in humans and is primarily excreted as unchanged drug in the
130 urine. Following oral administration, approximately 87% of an administered
131 dose was recovered as unchanged drug in urine within 48 hours, whereas less
132 than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an
133 administered dose was recovered in the urine as the desmethyl and N-oxide
134 metabolites, the only metabolites identified in humans. These metabolites have
135 little relevant pharmacological activity.

136
137 **Excretion**

138 Levofloxacin is excreted largely as unchanged drug in the urine. The mean
139 terminal plasma elimination half-life of levofloxacin ranges from approximately
140 6 to 8 hours following single or multiple doses of levofloxacin given orally or
141 intravenously. The mean apparent total body clearance and renal clearance
142 range from approximately 144 to 226 mL/min and 96 to 142 mL/min,
143 respectively. Renal clearance in excess of the glomerular filtration rate
144 suggests that tubular secretion of levofloxacin occurs in addition to its
145 glomerular filtration. Concomitant administration of either cimetidine or
146 probenecid results in approximately 24% and 35% reduction in the levofloxacin
147 renal clearance, respectively, indicating that secretion of levofloxacin occurs in
148 the renal proximal tubule. No levofloxacin crystals were found in any of the
149 urine samples freshly collected from subjects receiving levofloxacin.

150
151 **Special Populations**

152 **Geriatric:** There are no significant differences in levofloxacin pharmacokinetics
153 between young and elderly subjects when the subjects' differences in
154 creatinine clearance are taken into consideration. Following a 500 mg oral dose
155 of levofloxacin to healthy elderly subjects (66 - 80 years of age), the mean
156 terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as
157 compared to approximately 6 hours in younger adults. The difference was
158 attributable to the variation in renal function status of the subjects and was not
159 believed to be clinically significant. Drug absorption appears to be unaffected
160 by age. Levofloxacin dose adjustment based on age alone is not necessary.

161
162 **Pediatric:** The pharmacokinetics of levofloxacin in pediatric subjects have not
163 been studied.

164
165 **Gender:** There are no significant differences in levofloxacin pharmacokinetics
166 between male and female subjects when subjects' differences in creatinine
167 clearance are taken into consideration. Following a 500 mg oral dose of
168 levofloxacin to healthy male subjects, the mean terminal plasma elimination
169 half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1
170 hours in female subjects. This difference was attributable to the variation in
171 renal function status of the male and female subjects and was not believed to
172 be clinically significant. Drug absorption appears to be unaffected by the

173 gender of the subjects. Dose adjustment based on gender alone is not
174 necessary.

175

176 **Race:** The effect of race on levofloxacin pharmacokinetics was examined
177 through a covariate analysis performed on data from 72 subjects: 48 white and
178 24 nonwhite. The apparent total body clearance and apparent volume of
179 distribution were not affected by the race of the subjects.

180

181 **Renal insufficiency:** Clearance of levofloxacin is substantially reduced and
182 plasma elimination half-life is substantially prolonged in patients with impaired
183 renal function (creatinine clearance <50mL/min), requiring dosage adjustment
184 in such patients to avoid accumulation. Neither hemodialysis nor continuous
185 ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin
186 from the body, indicating that supplemental doses of levofloxacin are not
187 required following hemodialysis or CAPD. (See **PRECAUTIONS: General** and
188 **DOSAGE AND ADMINISTRATION.**)

189

190 **Hepatic insufficiency:** Pharmacokinetic studies in hepatically impaired
191 patients have not been conducted. Due to the limited extent of levofloxacin
192 metabolism, the pharmacokinetics of levofloxacin are not expected to be
193 affected by hepatic impairment.

194

195 **Bacterial infection:** The pharmacokinetics of levofloxacin in patients with
196 serious community-acquired bacterial infections are comparable to those
197 observed in healthy subjects.

198

199 **Drug-drug interactions:** The potential for pharmacokinetic drug interactions
200 between levofloxacin and theophylline, warfarin, cyclosporine, digoxin,
201 probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See
202 **PRECAUTIONS: Drug Interactions.**)

203

204

205

Table 1. Mean ±SD Levofloxacin PK Parameters

Regimen	C _{max} (mg/mL)	T _{max} (h)	AUC (mg·h/mL)	CL/F ¹ (mL/min)	Vd/F ² (L)	t _{1/2} (h)	CL _R (mL/min)
Single dose							
250 mg p.o. ³	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg p.o. ^{3*}	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg i.v. ³	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg p.o. ^{5*}	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg i.v. ⁵	11.5 ± 4.0	ND	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg q24h p.o. ³	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v. ³	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg q24h i.v., patients with bacterial infection ⁴⁶	8.7 ± 4.0 ⁷	ND	72.5 ± 51.2 ⁷	154 ± 72	111 ± 58	ND	ND
750 mg q24h p.o. ⁵	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg q24h i.v. ⁵	12.1 ± 4.1 ⁴	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg p.o. single dose, effects of gender and age:							
male ⁸	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female ⁹	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
young ¹⁰	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly ¹¹	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg p.o. single dose, patients with renal insufficiency:							
CL _{CR} 50-80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CL _{CR} 20-49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CL _{CR} <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

¹ clearance/bioavailability

² volume of distribution/bioavailability

³ healthy males 18-53 years of age

⁴ 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

⁵ healthy male and female subjects 18-54 years of age¹

⁶ 500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin

⁷ dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

⁸ healthy males 22-75 years of age

⁹ healthy females 18-80 years of age

¹⁰ young healthy male and female subjects 18-36 years of age

¹¹ healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; $F = 0.99 \pm 0.08$ from a 500-mg tablet and $F = 0.99 \pm 0.06$ from a 750-mg tablet ; ND = not determined.

206 **MICROBIOLOGY**

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

213

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

217

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

222

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

227

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

231

232 **Aerobic gram-positive microorganisms**

233 *Enterococcus faecalis* (many strains are only moderately susceptible)

234 *Staphylococcus aureus* (methicillin-susceptible strains)

235 *Staphylococcus saprophyticus*

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

237 *Streptococcus pyogenes*

238

239 *Note: penicillin-resistant *S. pneumoniae* are those strains with a penicillin MIC
240 value of — 2 μ g/mL

241

242 **Aerobic gram-negative microorganisms**

243 *Enterobacter cloacae*

244 *Escherichia coli*

245 *Haemophilus influenzae*

246 *Haemophilus parainfluenzae*

247 *Klebsiella pneumoniae*

248 *Legionella pneumophila*

249 *Moraxella catarrhalis*

250 *Proteus mirabilis*

251 *Pseudomonas aeruginosa*

252

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

255

256 **Other microorganisms**

257 *Chlamydia pneumoniae*

258 *Mycoplasma pneumoniae*

259

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

262

263 Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of
264 2 µg/mL or less against most (≥90%) strains of the following microorganisms;
265 however, the safety and effectiveness of levofloxacin in treating clinical
266 infections due to these microorganisms have not been established in adequate
267 and well-controlled trials.

268

269 **Aerobic gram-positive microorganisms**

270 *Staphylococcus epidermidis* (methicillin-susceptible strains)

271 *Streptococcus* (Group C/F)

272 *Streptococcus* (Group G)

273 *Streptococcus agalactiae*

274 *Streptococcus milleri*

275 Viridans group streptococci

276

277 **Aerobic gram-negative microorganisms**

278 *Acinetobacter baumannii*

279 *Acinetobacter lwoffii*

280 *Bordetella pertussis*

281 *Citrobacter (diversus) koseri*

282 *Citrobacter freundii*

283 *Enterobacter aerogenes*

284 *Enterobacter sakazakii*

285 *Klebsiella oxytoca*

286 *Morganella morganii*

287 *Pantoea (Enterobacter) agglomerans*

288 *Proteus vulgaris*

289 *Providencia rettgeri*

290 *Providencia stuartii*

291 *Pseudomonas fluorescens*

292 *Serratia marcescens*

293

294 **Anaerobic gram-positive microorganisms**

295 *Clostridium perfringens*

296

297 **Susceptibility Tests**

298 Susceptibility testing for levofloxacin should be performed, as it is the optimal
299 predictor of activity.

300

301 **Dilution techniques:** Quantitative methods are used to determine
302 antimicrobial minimal inhibitory concentrations (MIC values). These MIC values
303 provide estimates of the susceptibility of bacteria to antimicrobial compounds.

304 The MIC values should be determined using a standardized procedure.
305 Standardized procedures are based on a dilution method¹ (broth or agar) or
306 equivalent with standardized inoculum concentrations and standardized
307 concentrations of levofloxacin powder. The MIC values should be interpreted
308 according to the following criteria:

309
310 For testing aerobic microorganisms other than *Haemophilus influenzae*,
311 *Haemophilus parainfluenzae*, and *Streptococcus* spp. including *S.*
312 *pneumoniae*:

313

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

314

315 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*.^a

316

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤2	Susceptible (S)

317

318 ^a These interpretive standards are applicable only to broth microdilution
319 susceptibility testing with *Haemophilus influenzae* and *Haemophilus*
320 *parainfluenzae* using Haemophilus Test Medium.¹

321

322 The current absence of data on resistant strains precludes defining any
323 categories other than "Susceptible". Strains yielding MIC results suggestive of
324 a "nonsusceptible" category should be submitted to a reference laboratory for
325 further testing.

326

327 For testing *Streptococcus* spp. including *S. pneumoniae*.^b

328

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

329

330 ^b These interpretive standards are applicable only to broth microdilution
331 susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed
332 horse blood.

333

334 A report of "Susceptible" indicates that the pathogen is likely to be inhibited if
335 the antimicrobial compound in the blood reaches the concentrations usually
336 achievable. A report of "Intermediate" indicates that the result should be
337 considered equivocal, and, if the microorganism is not fully susceptible to
338 alternative, clinically feasible drugs, the test should be repeated. This category
339 implies possible clinical applicability in body sites where the drug is
340 physiologically concentrated or in situations where a high dosage of drug can be
341 used. This category also provides a buffer zone which prevents small

342 uncontrolled technical factors from causing major discrepancies in
343 interpretation. A report of "Resistant" indicates that the pathogen is not likely to
344 be inhibited if the antimicrobial compound in the blood reaches the
345 concentrations usually achievable; other therapy should be selected.

346
347 Standardized susceptibility test procedures require the use of laboratory control
348 microorganisms to control the technical aspects of the laboratory procedures.
349 Standard levofloxacin powder should give the following MIC values:

350
351

<u>Microorganism</u>		<u>MIC (µg/mL)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.25 - 2
<i>Escherichia coli</i>	ATCC 25922	0.008 - 0.06
<i>Escherichia coli</i>	ATCC 35218	0.015 - 0.06
<i>Pseudomonas aeruginosa</i>	ATCC 27853	0.5 - 4
<i>Staphylococcus aureus</i>	ATCC 29213	0.06 - 0.5
<i>Haemophilus influenzae</i>	ATCC 49247 ^c	0.008 - 0.03
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^d	0.5 - 2

352

353 ^c This quality control range is applicable to only *H. influenzae* ATCC 49247
354 tested by a broth microdilution procedure using Haemophilus Test Medium
355 (HTM).¹

356

357 ^d This quality control range is applicable to only *S. pneumoniae* ATCC 49619
358 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton
359 broth with 2-5% lysed horse blood.

360

361 **Diffusion techniques:** Quantitative methods that require measurement of
362 zone diameters also provide reproducible estimates of the susceptibility of
363 bacteria to antimicrobial compounds. One such standardized procedure²
364 requires the use of standardized inoculum concentrations. This procedure uses
365 paper disks impregnated with 5-µg levofloxacin to test the susceptibility of mi-
366 croorganisms to levofloxacin.

367

368 Reports from the laboratory providing results of the standard single-disk
369 susceptibility test with a 5-µg levofloxacin disk should be interpreted according
370 to the following criteria:

371

372 For aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus*
373 *parainfluenzae*, and *Streptococcus* spp. including *S. pneumoniae*:

374

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

375

376 For *Haemophilus influenzae* and *Haemophilus parainfluenzae*.^e

377

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥17	Susceptible (S)

378

379 ^e These interpretive standards are applicable only to disk diffusion susceptibility
380 testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using
381 Haemophilus Test Medium.²

382

383 The current absence of data on resistant strains precludes defining any
384 categories other than "Susceptible". Strains yielding zone diameter results
385 suggestive of a "nonsusceptible" category should be submitted to a reference
386 laboratory for further testing.

387

388 For *Streptococcus* spp. including *S. pneumoniae*.^f

389

<u>Zone diameter (mm)</u>	<u>Interpretation</u>
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

390

391 ^f These zone diameter standards for *Streptococcus* spp. including *S.*
392 *pneumoniae* apply only to tests performed using Mueller-Hinton agar
393 supplemented with 5% sheep blood and incubated in 5% CO₂.

394

395 Interpretation should be as stated above for results using dilution techniques.
396 Interpretation involves correlation of the diameter obtained in the disk test with
397 the MIC for levofloxacin.

398

399 As with standardized dilution techniques, diffusion methods require the use of
400 laboratory control microorganisms to control the technical aspects of the
401 laboratory procedures. For the diffusion technique, the 5-μg levofloxacin disk
402 should provide the following zone diameters in these laboratory test quality
403 control strains:

404

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	29 - 37
<i>Pseudomonas aeruginosa</i>	ATCC 27853	19 - 26
<i>Staphylococcus aureus</i>	ATCC 25923	25 - 30
<i>Haemophilus influenzae</i>	ATCC 49247 ^g	32 - 40
<i>Streptococcus pneumoniae</i>	ATCC 49619 ^h	20 - 25

405

406 ^g This quality control range is applicable to only *H. influenzae* ATCC 49247
407 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM).²

408

409 ^h This quality control range is applicable to only *S. pneumoniae* ATCC 49619
410 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented
411 with 5% sheep blood and incubated in 5% CO₂.

412

413 **INDICATIONS AND USAGE**

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

421

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

424

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

428

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

435

436 **Complicated skin and skin structure infections** due to methicillin-sensitive
437 *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, or,
438 *Proteus mirabilis*.

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

442

443 **Complicated urinary tract infections** (mild to moderate) due to *Enterococcus*
444 *faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*,
445 *Proteus mirabilis*, or *Pseudomonas aeruginosa*.

446

447 **Acute pyelonephritis** (mild to moderate) caused by *Escherichia coli*.

448

449 **Uncomplicated urinary tract infections** (mild to moderate) due to
450 *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*.

451

452 Appropriate culture and susceptibility tests should be performed before
453 treatment in order to isolate and identify organisms causing the infection and to
454 determine their susceptibility to levofloxacin. Therapy with levofloxacin may be
455 initiated before results of these tests are known; once results become
456 available, appropriate therapy should be selected.

457

458 As with other drugs in this class, some strains of *Pseudomonas aeruginosa*
459 may develop resistance fairly rapidly during treatment with levofloxacin. Culture
460 and susceptibility testing performed periodically during therapy will provide

461 information about the continued susceptibility of the pathogens to the
462 antimicrobial agent and also the possible emergence of bacterial resistance.

463

464 **CONTRAINDICATIONS**

465 Levofloxacin is contraindicated in persons with a history of hypersensitivity to
466 levofloxacin, quinolone antimicrobial agents, or any other components of this
467 product.

468

469 **WARNINGS**

470 **THE SAFETY AND EFFICACY OF LEVOFLOXACIN IN PEDIATRIC**
471 **PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS),**
472 **PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN**
473 **ESTABLISHED.** (See **PRECAUTIONS: Pediatric Use, Pregnancy, and**
474 **Nursing Mothers** subsections.)

475

476 In immature rats and dogs, the oral and intravenous administration of
477 levofloxacin increased the incidence and severity of osteochondrosis. Other
478 fluoroquinolones also produce similar erosions in the weight bearing joints and
479 other signs of arthropathy in immature animals of various species. (See
480 **ANIMAL PHARMACOLOGY.**)

481

482 Convulsions and toxic psychoses have been reported in patients receiving
483 quinolones, including levofloxacin. Quinolones may also cause increased
484 intracranial pressure and central nervous system stimulation which may lead to
485 tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations,
486 paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or
487 acts. These reactions may occur following the first dose. If these reactions
488 occur in patients receiving levofloxacin, the drug should be discontinued and
489 appropriate measures instituted. As with other quinolones, levofloxacin should
490 be used with caution in patients with a known or suspected CNS disorder that
491 may predispose to seizures or lower the seizure threshold (e.g., severe
492 cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that
493 may predispose to seizures or lower the seizure threshold (e.g., certain drug
494 therapy, renal dysfunction.) (See **PRECAUTIONS: General, Information for**
495 **Patients, Drug Interactions and ADVERSE REACTIONS.**)

496

497 Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions
498 have been reported in patients receiving therapy with quinolones, including
499 levofloxacin. These reactions often occur following the first dose. Some
500 reactions have been accompanied by cardiovascular collapse,
501 hypotension/shock, seizure, loss of consciousness, tingling, angioedema
502 (including tongue, laryngeal, throat, or facial edema/swelling), airway
503 obstruction (including bronchospasm, shortness of breath, and acute
504 respiratory distress), dyspnea, urticaria, itching, and other serious skin
505 reactions. Levofloxacin should be discontinued immediately at the first
506 appearance of a skin rash or any other sign of hypersensitivity. Serious acute
507 hypersensitivity reactions may require treatment with epinephrine and other
508 resuscitative measures, including oxygen, intravenous fluids, antihistamines,

509 corticosteroids, pressor amines, and airway management, as clinically
510 indicated. (See **PRECAUTIONS** and **ADVERSE REACTIONS**.)

511

512 Serious and sometimes fatal events, some due to hypersensitivity, and some
513 due to uncertain etiology, have been reported rarely in patients receiving
514 therapy with quinolones, including levofloxacin. These events may be severe
515 and generally occur following the administration of multiple doses. Clinical
516 manifestations may include one or more of the following: fever, rash or severe
517 dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson
518 Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic
519 pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis;
520 jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and
521 aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura;
522 leukopenia; agranulocytosis; pancytopenia; and/or other hematologic
523 abnormalities. The drug should be discontinued immediately at the first
524 appearance of a skin rash or any other sign of hypersensitivity and supportive
525 measures instituted. (See **PRECAUTIONS: Information for Patients** and
526 **ADVERSE REACTIONS**.)

527

528 **Pseudomembranous colitis has been reported with nearly all antibacterial**
529 **agents, including levofloxacin, and may range in severity from mild to**
530 **life-threatening. Therefore, it is important to consider this diagnosis in**
531 **patients who present with diarrhea subsequent to the administration of**
532 **any antibacterial agent.**

533

534 Treatment with antibacterial agents alters the normal flora of the colon and may
535 permit overgrowth of clostridia. Studies indicate that a toxin produced by
536 *Clostridium difficile* is one primary cause of "antibiotic-associated colitis".

537

538 After the diagnosis of pseudomembranous colitis has been established,
539 therapeutic measures should be initiated. Mild cases of pseudomembranous
540 colitis usually respond to drug discontinuation alone. In moderate to severe
541 cases, consideration should be given to management with fluids and
542 electrolytes, protein supplementation, and treatment with an antibacterial drug
543 clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS**.)

544

545 Ruptures of the shoulder, hand, or Achilles tendons that required surgical
546 repair or resulted in prolonged disability have been reported in patients
547 receiving quinolones, including levofloxacin. Levofloxacin should be
548 discontinued if the patient experiences pain, inflammation, or rupture of a
549 tendon. Patients should rest and refrain from exercise until the diagnosis of
550 tendinitis or tendon rupture has been confidently excluded. Tendon rupture can
551 occur during or after therapy with quinolones, including levofloxacin.

552

553 **PRECAUTIONS**

554 **General**

555 Because a rapid or bolus intravenous injection may result in hypotension,
556 LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW

557 INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES.
558 DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION.**)

559

560 Although levofloxacin is more soluble than other quinolones, adequate
561 hydration of patients receiving levofloxacin should be maintained to prevent the
562 formation of a highly concentrated urine.

563

564 Administer levofloxacin with caution in the presence of renal insufficiency.
565 Careful clinical observation and appropriate laboratory studies should be
566 performed prior to and during therapy since elimination of levofloxacin may be
567 reduced. In patients with impaired renal function (creatinine clearance
568 <50 mL/min), adjustment of the dosage regimen is necessary to avoid the
569 accumulation of levofloxacin due to decreased clearance. (See **CLINICAL**
570 **PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION.**)

571

572 Moderate to severe phototoxicity reactions have been observed in patients
573 exposed to direct sunlight while receiving drugs in this class. Excessive
574 exposure to sunlight should be avoided. However, in clinical trials with
575 levofloxacin, phototoxicity has been observed in less than 0.1% of patients.
576 Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

577

578 As with other quinolones, levofloxacin should be used with caution in any
579 patient with a known or suspected CNS disorder that may predispose to
580 seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis,
581 epilepsy) or in the presence of other risk factors that may predispose to
582 seizures or lower the seizure threshold (e.g., certain drug therapy, renal
583 dysfunction). (See **WARNINGS** and **Drug Interactions.**)

584

585 As with other quinolones, disturbances of blood glucose, including symptomatic
586 hyper- and hypoglycemia, have been reported, usually in diabetic patients
587 receiving concomitant treatment with an oral hypoglycemic agent (e.g.,
588 glyburide/glibenclamide) or with insulin. In these patients, careful monitoring of
589 blood glucose is recommended. If a hypoglycemic reaction occurs in a patient
590 being treated with levofloxacin, levofloxacin should be discontinued
591 immediately and appropriate therapy should be initiated immediately. (See
592 **Drug Interactions** and **ADVERSE REACTIONS.**)

593

594 Some quinolones have been associated with prolongation of the QT interval on
595 the electrocardiogram and infrequent cases of arrhythmia. During post-
596 marketing surveillance, extremely rare cases of torsades de pointes, have been
597 reported in patients taking levofloxacin. These reports generally involve
598 patients who had other concurrent medical conditions and the relationship to
599 levofloxacin has not been established. Among drugs known to cause
600 prolongation of the QT interval, the risk of arrhythmias may be reduced by
601 avoiding use in the presence of hypokalemia, significant bradycardia, or
602 concurrent treatment with class Ia or class III antiarrhythmic agents.

603

604 As with any potent antimicrobial drug, periodic assessment of organ system
605 functions, including renal, hepatic, and hematopoietic, is advisable during
606 therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

607

608 **Information for Patients**

609 Patients should be advised:

- 610 • to drink fluids liberally;
- 611 • that antacids containing magnesium, or aluminum, as well as sucralfate,
612 metal cations such as iron, and multivitamin preparations with zinc or
613 Videx[®], (Didanosine), chewable/buffered tablets or the pediatric powder for
614 oral solution should be taken at least two hours before or two hours after
615 oral levofloxacin administration. (See **Drug Interactions**);
- 616 • that oral levofloxacin can be taken without regard to meals;
- 617 • that levofloxacin may cause neurologic adverse effects (e.g., dizziness,
618 lightheadedness) and that patients should know how they react to
619 levofloxacin before they operate an automobile or machinery or engage in
620 other activities requiring mental alertness and coordination. (See
621 **WARNINGS** and **ADVERSE REACTIONS**);
- 622 • to discontinue treatment and inform their physician if they experience pain,
623 inflammation, or rupture of a tendon, and to rest and refrain from exercise
624 until the diagnosis of tendinitis or tendon rupture has been confidently
625 excluded;
- 626 • that levofloxacin may be associated with hypersensitivity reactions, even
627 following the first dose, and to discontinue the drug at the first sign of a skin
628 rash, hives or other skin reactions, a rapid heartbeat, difficulty in
629 swallowing or breathing, any swelling suggesting angioedema (e.g.,
630 swelling of the lips, tongue, face, tightness of the throat, hoarseness), or
631 other symptoms of an allergic reaction. (See **WARNINGS** and **ADVERSE**
632 **REACTIONS**);
- 633 • to avoid excessive sunlight or artificial ultraviolet light while receiving
634 levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption)
635 occurs;
- 636 • that if they are diabetic and are being treated with insulin or an oral
637 hypoglycemic agent and a hypoglycemic reaction occurs, they should
638 discontinue levofloxacin and consult a physician. (See **PRECAUTIONS:**
639 **General** and **Drug Interactions**.);
- 640 • that concurrent administration of warfarin and levofloxacin has been
641 associated with increases of the International Normalized Ratio (INR) or
642 prothrombin time and clinical episodes of bleeding. Patients should notify
643 their physician if they are taking warfarin.
- 644 • that convulsions have been reported in patients taking quinolones, including
645 levofloxacin, and to notify their physician before taking this drug if there is a
646 history of this condition.

647

648 **Drug Interactions**

649 **Antacids, Sucralfate, Metal Cations, Multivitamins**

650 LEVAQUIN Tablets: While the chelation by divalent cations is less marked than
651 with other quinolones, concurrent administration of LEVAQUIN Tablets with

652 antacids containing magnesium, or aluminum, as well as sucralfate, metal
653 cations such as iron, and multivitamin preparations with zinc may interfere with
654 the gastrointestinal absorption of levofloxacin, resulting in systemic levels
655 considerably lower than desired. Tablets with antacids containing magnesium,
656 aluminum, as well as sucralfate, metal cations such as iron, and multivitamins
657 preparations with zinc or Videx[®], (Didanosine), chewable/buffered tablets or the
658 pediatric powder for oral solution may substantially interfere with the
659 gastrointestinal absorption of levofloxacin, resulting in systemic levels
660 considerably lower than desired. These agents should be taken at least two
661 hours before or two hours after levofloxacin administration.

662
663 LEVAQUIN Injection: There are no data concerning an interaction of
664 **Intravenous** quinolones with **oral** antacids, sucralfate, multivitamins, Videx[®],
665 (Didanosine), or metal cations. However, no quinolone should be
666 co-administered with any solution containing multivalent cations, e.g.,
667 magnesium, through the same intravenous line. (See **DOSAGE AND**
668 **ADMINISTRATION.**)

669
670 **Theophylline:** No significant effect of levofloxacin on the plasma
671 concentrations, AUC, and other disposition parameters for theophylline was
672 detected in a clinical study involving 14 healthy volunteers. Similarly, no
673 apparent effect of theophylline on levofloxacin absorption and disposition was
674 observed. However, concomitant administration of other quinolones with
675 theophylline has resulted in prolonged elimination half-life, elevated serum
676 theophylline levels, and a subsequent increase in the risk of theophylline-
677 related adverse reactions in the patient population. Therefore, theophylline
678 levels should be closely monitored and appropriate dosage adjustments made
679 when levofloxacin is co-administered. Adverse reactions, including seizures,
680 may occur with or without an elevation in serum theophylline levels. (See
681 **WARNINGS** and **PRECAUTIONS: General.**)

682
683 **Warfarin:** No significant effect of levofloxacin on the peak plasma
684 concentrations, AUC, and other disposition parameters for R- and S- warfarin
685 was detected in a clinical study involving healthy volunteers. Similarly, no
686 apparent effect of warfarin on levofloxacin absorption and disposition was
687 observed. There have been reports during the post-marketing experience in
688 patients that levofloxacin enhances the effects of warfarin. Elevations of the
689 prothrombin time in the setting of concurrent warfarin and levofloxacin use
690 have been associated with episodes of bleeding. Prothrombin time,
691 International Normalized Ratio (INR), or other suitable anticoagulation tests
692 should be closely monitored if levofloxacin is administered concomitantly with
693 warfarin. Patients should also be monitored for evidence of bleeding.

694
695 **Cyclosporine:** No significant effect of levofloxacin on the peak plasma
696 concentrations, AUC, and other disposition parameters for cyclosporine was
697 detected in a clinical study involving healthy volunteers. However, elevated
698 serum levels of cyclosporine have been reported in the patient population when
699 co-administered with some other quinolones. Levofloxacin C_{max} and k_e were

700 slightly lower while T_{max} and $t_{1/2}$ were slightly longer in the presence of
701 cyclosporine than those observed in other studies without concomitant
702 medication. The differences, however, are not considered to be clinically
703 significant. Therefore, no dosage adjustment is required for levofloxacin or
704 cyclosporine when administered concomitantly.

705
706 **Digoxin:** No significant effect of levofloxacin on the peak plasma
707 concentrations, AUC, and other disposition parameters for digoxin was
708 detected in a clinical study involving healthy volunteers. Levofloxacin
709 absorption and disposition kinetics were similar in the presence or absence of
710 digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required
711 when administered concomitantly.

712
713 **Probenecid and Cimetidine:** No significant effect of probenecid or cimetidine
714 on the rate and extent of levofloxacin absorption was observed in a clinical
715 study involving healthy volunteers. The AUC and $t_{1/2}$ of levofloxacin were 27-
716 38% and 30% higher, respectively, while CL/F and CL_R were 21-35% lower
717 during concomitant treatment with probenecid or cimetidine compared to
718 levofloxacin alone. Although these differences were statistically significant, the
719 changes were not high enough to warrant dosage adjustment for levofloxacin
720 when probenecid or cimetidine is co-administered.

721
722 **Non-steroidal anti-inflammatory drugs:** The concomitant administration of a
723 non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin,
724 may increase the risk of CNS stimulation and convulsive seizures. (See
725 **WARNINGS** and **PRECAUTIONS: General**.)

726
727 **Antidiabetic agents:** Disturbances of blood glucose, including hyperglycemia
728 and hypoglycemia, have been reported in patients treated concomitantly with
729 quinolones and an antidiabetic agent. Therefore, careful monitoring of blood
730 glucose is recommended when these agents are co-administered.

731
732 **Carcinogenesis, Mutagenesis, Impairment of Fertility**
733 In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential
734 following daily dietary administration for 2 years; the highest dose (100
735 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg)
736 based upon relative body surface area.

737
738 Levofloxacin was not mutagenic in the following assays; Ames bacterial
739 mutation assay (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation
740 assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled
741 DNA synthesis assay, and the mouse sister chromatid exchange assay. It was
742 positive in the in vitro chromosomal aberration (CHL cell line) and sister
743 chromatid exchange (CHL/IU cell line) assays.

744
745 Levofloxacin caused no impairment of fertility or reproductive performance in
746 rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the
747 highest recommended human dose based upon relative body surface area and

748 intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the
749 highest recommended human dose based upon relative body surface area.

750

751 **Pregnancy: Teratogenic Effects. Pregnancy Category C.**

752 Levofloxacin was not teratogenic in rats at oral doses as high as
753 810 mg/kg/day which corresponds to 9.4 times the highest recommended
754 human dose based upon relative body surface area, or at intravenous doses as
755 high as 160 mg/kg/day corresponding to 1.9 times the highest recommended
756 human dose based upon relative body surface area. The oral dose of
757 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal
758 mortality. No teratogenicity was observed when rabbits were dosed orally as
759 high as 50 mg/kg/day which corresponds to 1.1 times the highest
760 recommended human dose based upon relative body surface area, or when
761 dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the
762 highest recommended human dose based upon relative body surface area.

763

764 There are, however, no adequate and well-controlled studies in pregnant
765 women. Levofloxacin should be used during pregnancy only if the potential
766 benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

767

768 **Nursing Mothers**

769 Levofloxacin has not been measured in human milk. Based upon data from
770 ofloxacin, it can be presumed that levofloxacin will be excreted in human milk.
771 Because of the potential for serious adverse reactions from levofloxacin in
772 nursing infants, a decision should be made whether to discontinue nursing or to
773 discontinue the drug, taking into account the importance of the drug to the
774 mother.

775

776 **Pediatric Use**

777 Safety and effectiveness in pediatric patients and adolescents below the age of
778 18 years have not been established. Quinolones, including levofloxacin, cause
779 arthropathy and osteochondrosis in juvenile animals of several species. (See
780 **WARNINGS**.)

781

782 **Geriatric Use**

783 In phase 3 clinical trials, 1,190 levofloxacin-treated patients (25%) were ≥ 65
784 years of age. Of these, 675 patients (14%) were between the ages of 65 and
785 74 and 515 patients (11%) were 75 years or older. No overall differences in
786 safety or effectiveness were observed between these subjects and younger
787 subjects, and other reported clinical experience has not identified differences in
788 responses between the elderly and younger patients, but greater sensitivity of
789 some older individuals cannot be ruled out.

790

791 The pharmacokinetic properties of levofloxacin in younger adults and elderly
792 adults do not differ significantly when creatinine clearance is taken into
793 consideration. However since the drug is known to be substantially excreted by
794 the kidney, the risk of toxic reactions to this drug may be greater in patients
795 with impaired renal function. Because elderly patients are more likely to have

796 decreased renal function, care should be taken in dose selection, and it may be
797 useful to monitor renal function.

798

799

ADVERSE REACTIONS

800 The incidence of drug-related adverse reactions in patients during Phase 3
801 clinical trials conducted in North America was 6.3%. Among patients receiving
802 levofloxacin therapy, 3.9% discontinued levofloxacin therapy due to adverse
803 experiences. [The overall incidence, type and distribution of adverse events](#)
804 [was similar in patients receiving levofloxacin doses of 750 mg once daily](#)
805 [compared to patients receiving doses of from 250 mg once daily to 500 mg](#)
806 [twice daily.](#)

807

808 In clinical trials, the following events were considered likely to be drug-related in
809 patients receiving levofloxacin:

810 nausea 1.3%, diarrhea 1.0%, vaginitis 0.7%, insomnia 0.5%, abdominal
811 pain 0.4%, flatulence 0.4%, pruritus 0.4%, dizziness 0.3%, dyspepsia 0.3%,
812 rash 0.3%, genital moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%,
813 constipation 0.1%, fungal infection 0.1%, genital pruritis 0.1%, headache 0.1%,
814 moniliasis 0.1%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%.

815

816 In clinical trials, the following events occurred in >3% of patients, regardless of
817 drug relationship:

818 nausea 7.2%, headache 6.4%, diarrhea 5.6%, insomnia 4/6%, injection site
819 reaction 3.5%, constipation 3.2%.

820

821 In clinical trials, the following events occurred in 1 to 3% of patients, regardless
822 of drug relationship:

823 dizziness 2.7%, abdominal pain 2.5%, dyspepsia 2.4%, vomiting 2.3%,
824 vaginitis 1.8%, injection site pain 1.7%, flatulence 1.5%, pain 1.4%,
825 pruritus 1.3%, sinusitis 1.3%, chest pain 1.2%, fatigue 1.2%, rash 1.2%, back
826 pain 1.1%, injection site inflammation 1.1%, rhinitis 1.0%, taste perversion
827 1.0%.

828

829

830 In clinical trials, the following events, of potential medical importance, occurred
831 at a rate of less than 1.0% regardless of drug relationship:

832

Autonomic Nervous System Disorders:	postural hypotension
Body as a Whole – General Disorders:	asthenia, edema, fever, malaise, rigors, substernal chest pain, syncope
Cardiovascular Disorders, General:	cardiac failure, circulatory failure, hypertension, hypotension
Central and Peripheral Nervous System Disorders:	abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoaesthesia, involuntary muscle contractions, paraesthesia, paralysis, speech disorder, stupor, tremor, vertigo
Gastro-Intestinal System Disorders:	dry mouth, dysphagia, gastroenteritis, G.I. hemorrhage, pancreatitis, pseudomembranous colitis, tongue edema
Hearing and Vestibular Disorders:	ear disorder (not otherwise specified), tinnitus
Heart Rate and Rhythm Disorders:	arrhythmia, atrial fibrillation, bradycardia, cardiac

	arrest, heart block, palpitation, supraventricular tachycardia, tachycardia, ventricular fibrillation
Liver and Biliary System Disorders:	abnormal hepatic function, cholelithiasis, hepatic coma, jaundice
Metabolic and Nutritional Disorders:	aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, increased LDH, weight decrease
Musculo-Skeletal System Disorders:	arthralgia, arthritis, arthrosis, muscle weakness, myalgia, osteomyelitis, rhabdomyolysis, synovitis, tendinitis
Myo, Endo, Pericardial and Valve Disorders:	angina pectoris, coronary thrombosis, myocardial infarction
Neoplasms:	carcinoma
Other Special Senses Disorders:	parosmia
Platelet, Bleeding and Clotting Disorders:	abnormal platelets, embolism (blood clot), epistaxis, purpura, thrombocytopenia
Psychiatric Disorders:	abnormal dreaming, aggressive reaction, agitation, anorexia, anxiety, confusion, delirium, depression, emotional lability, hallucination, impaired concentration, impotence, manic reaction, mental deficiency, nervousness, paranoia, sleep disorder, somnolence, withdrawal syndrome
Red Blood Cell Disorders:	anemia
Reproductive Disorders:	ejaculation failure
Resistance Mechanism Disorders:	fungal infection, genital moniliasis
Respiratory System Disorders:	ARDS, asthma, coughing, dyspnea, haemoptysis, hypoxia, pleural effusion, respiratory insufficiency
Skin and Appendages Disorders:	erythema nodosum, genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration, urticaria
Urinary System Disorders:	abnormal renal function, acute renal failure, face edema, haematuria
Vascular (Extracardiac) Disorders:	cerebrovascular disorder, phlebitis
Vision Disorders:	abnormal vision, conjunctivitis, diplopia
White Cell and RES Disorders:	granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, WBC abnormal (not otherwise specified)

833

834

835 In clinical trials using multiple-dose therapy, ophthalmologic abnormalities,
836 including cataracts and multiple punctate lenticular opacities, have been noted

837 in patients undergoing treatment with other quinolones. The relationship of the
838 drugs to these events is not presently established.

839

840 Crystalluria and cylindruria have been reported with other quinolones.

841

842 The following laboratory abnormalities appeared in 2.2% of patients receiving
843 levofloxacin. It is not known whether these abnormalities were caused by the
844 drug or the underlying condition being treated.

845

846 Blood Chemistry: decreased glucose

847 Hematology: decreased lymphocytes

848

849 **Post-Marketing Adverse Reactions**

850 Additional adverse events reported from worldwide post-marketing experience
851 with levofloxacin include:

852 allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia,
853 abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic
854 anemia, multi-system organ failure, increased International Normalized Ratio
855 (INR)/prothrombin time, Stevens-Johnson Syndrome, tendon rupture, torsades
856 de pointes, vasodilation.

857

858

859 **OVERDOSAGE**

860 Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and
861 monkeys exhibited the following clinical signs after receiving a single high dose
862 of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea,
863 prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally
864 and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an
865 acute overdose, the stomach should be emptied. The patient should be
866 observed and appropriate hydration maintained. Levofloxacin is not efficiently
867 removed by hemodialysis or peritoneal dialysis.

868

869 **DOSAGE AND ADMINISTRATION**

870 LEVAQUIN Injection should only be administered by intravenous infusion. It is
871 not for intramuscular, intrathecal, intraperitoneal, or subcutaneous
872 administration.

873

874 **CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE**
875 **AVOIDED.** Levofloxacin Injection should be infused intravenously slowly over a
876 period of not less than 60 or 90 minutes, depending on the dosage. (See
877 **PRECAUTIONS.**)

878

879 **Single-use vials require dilution prior to administration.** (See
880 **PREPARATION FOR ADMINISTRATION.**)

881

882 The usual dose of LEVAQUIN Tablets/Injection is 250 mg or 500 mg
883 administered orally or by slow infusion over 60 minutes every 24 hours or
884 750 mg administered by slow infusion over 90 minutes every 24 h, as indicated

885 by infection and described in the following dosing chart. These
886 recommendations apply to patients with normal renal function (i.e., creatinine
887 clearance > 80 mL/min). For patients with altered renal function see the
888 **Patients with Impaired Renal Function** subsection. Oral doses should be
889 administered at least two hours before or two hours after antacids containing
890 magnesium, aluminum, as well as sucralfate, metal cations such as iron, and
891 multivitamin preparations with zinc or Videx[®], (Didanosine), chewable/buffered
892 tablets or the pediatric powder for oral solution.

893
894

Patients with Normal Renal Function

Infection*	Unit Dose	Freq.	Duration**	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10-14 days	500 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg

895 * **DUE TO THE DESIGNATED PATHOGENS** (See **INDICATIONS AND**
896 **USAGE.**)

897 ** Sequential therapy (intravenous to oral) may be instituted at the discretion of
898 the physician.

899
900

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis / Comm. Acquired Pneumonia / Acute Maxillary Sinusitis / Uncomplicated SSSI		
CL _{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL _{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL _{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI		
CL _{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL _{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL _{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI / Acute Pyelonephritis		

CL _{CR} ≥20 mL/min	No dosage adjustment required	
CL _{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR}=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

901

902 When only the serum creatinine is known, the following formula may be used to
903 estimate creatinine clearance.

904

905 Men: Creatinine Clearance (mL/min) =

906

907

908

$$\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

909

Women: 0.85 x the value calculated for men.

910

911 The serum creatinine should represent a steady state of renal function.

912

913 **Preparation of Levofloxacin Injection for Administration**

914 **LEVAQUIN Injection in Single-Use Vials:** LEVAQUIN Injection is supplied in
915 single-use vials containing a concentrated levofloxacin solution with the
916 equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in
917 Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of
918 levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST**
919 **BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO**
920 **INTRAVENOUS ADMINISTRATION.** (See **COMPATIBLE INTRAVENOUS**
921 **SOLUTIONS.**) The concentration of the resulting diluted solution should be
922 5 mg/mL prior to administration.

923

924 This intravenous drug product should be inspected visually for particulate
925 matter prior to administration. Samples containing visible particles should be
926 discarded.

927

928 Since no preservative or bacteriostatic agent is present in this product, aseptic
929 technique must be used in preparation of the final intravenous solution. **Since**
930 **the vials are for single-use only, any unused portion remaining in the vial**
931 **should be discarded. When used to prepare two 250 mg doses from the**
932 **20 mL vial containing 500 mg of levofloxacin, the full content of the vial**
933 **should be withdrawn at once using a single-entry procedure, and a**
934 **second dose should be prepared and stored for subsequent use.** (See
935 **Stability of LEVAQUIN Injection Following Dilution.**)

936

937 Since only limited data are available on the compatibility of levofloxacin
938 intravenous injection with other intravenous substances, **additives or other**
939 **medications should not be added to LEVAQUIN Injection in single-use**
940 **vials or infused simultaneously through the same intravenous line.** If the
941 same intravenous line is used for sequential infusion of several different drugs,

942 the line should be flushed before and after infusion of LEVAQUIN Injection with
943 an infusion solution compatible with LEVAQUIN Injection and with any other
944 drug(s) administered via this common line.

945

946 Prepare the desired dosage of levofloxacin according to the following chart:

947

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL (20 mL Vial)	40 mL	60 min
500 mg	20 mL (20 mL Vial)	80 mL	60 min
750 mg	30 mL (30 mL Vial)	120 mL	90 min

948 For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL),
949 withdraw 20 mL and dilute with a compatible intravenous solution to a total
950 volume of 100 mL.

951

952 Compatible Intravenous Solutions: Any of the following intravenous solutions
953 may be used to prepare a 5 mg/mL levofloxacin solution with the approximate
954 pH values:

955

<u>Intravenous Fluids</u>	<u>Final pH of LEVAQUIN Solution</u>
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte [®] 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

956

957 **LEVAQUIN Injection Premix in Single-Use Flexible Containers:**
958 LEVAQUIN Injection is also supplied in flexible containers containing a
959 premixed, ready-to-use levofloxacin solution in D₅W for single-use. The fill
960 volume is either 50 or 100 mL for the 100 mL flexible container or 150 mL for
961 the 150 mL container. **NO FURTHER DILUTION OF THESE PREPARATIONS**
962 **ARE NECESSARY. Consequently each 50 mL, 100 mL, and 150 mL**
963 **premix flexible container already contains a dilute solution with the**
964 **equivalent of 250 mg, 500 mg, and 750 mg of levofloxacin, respectively**
965 **(5 mg/mL) in 5% Dextrose (D₅W).**

966

967 This parenteral drug product should be inspected visually for particulate matter
968 prior to administration. Samples containing visible particles should be
969 discarded.

970

971 **Since the premix flexible containers are for single-use only, any unused**
972 **portion should be discarded.**

973

974 Since only limited data are available on the compatibility of levofloxacin
975 intravenous injection with other intravenous substances, **additives or other**
976 **medications should not be added to LEVAQUIN Injection in flexible**
977 **containers or infused simultaneously through the same intravenous line.**
978 If the same intravenous line is used for sequential infusion of several different
979 drugs, the line should be flushed before and after infusion of LEVAQUIN
980 Injection with an infusion solution compatible with LEVAQUIN Injection and with
981 any other drug(s) administered via this common line.

982

983 Instructions for the Use of LEVAQUIN Injection Premix in Flexible Containers

984 To open:

- 985 1. Tear outer wrap at the notch and remove solution container.
- 986 2. Check the container for minute leaks by squeezing the inner bag firmly. If
987 leaks are found, or if the seal is not intact, discard the solution, as the
988 sterility may be compromised.
- 989 3. Do not use if the solution is cloudy or a precipitate is present.
- 990 4. Use sterile equipment.
- 991 5. **WARNING: Do not use flexible containers in series connections.** Such
992 use could result in air embolism due to residual air being drawn from the
993 primary container before administration of the fluid from the secondary
994 container is complete.

995

996 Preparation for administration:

- 997 1. Close flow control clamp of administration set.
- 998 2. Remove cover from port at bottom of container.
- 999 3. Insert piercing pin of administration set into port with a twisting motion until
1000 the pin is firmly seated. **NOTE: See full directions on administration set**
1001 **carton.**
- 1002 4. Suspend container from hanger.
- 1003 5. Squeeze and release drip chamber to establish proper fluid level in
1004 chamber during infusion of LEVAQUIN Injection in Premix Flexible
1005 Containers.
- 1006 6. Open flow control clamp to expel air from set. Close clamp.
- 1007 7. Regulate rate of administration with flow control clamp.

1008

1009 **Stability of LEVAQUIN Injection as Supplied**

1010 When stored under recommended conditions, LEVAQUIN Injection, as
1011 supplied in 20 mL and 30 mL vials, or 100 mL and 150 mL flexible containers,
1012 is stable through the expiration date printed on the label.

1013

1014 **Stability of LEVAQUIN Injection Following Dilution**

1015 LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a
1016 concentration of 5 mg/mL, is stable for 72 h when stored at or below 25°C
1017 (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic
1018 intravenous containers. Solutions that are diluted in a compatible intravenous
1019 solution and frozen in glass bottles or plastic intravenous containers are stable
1020 for 6 months when stored at -20°C (-4°F). **THAW FROZEN SOLUTIONS AT**
1021 **ROOM TEMPERATURE 25°C (77°F) OR IN A REFRIGERATOR 8°C (46°F).**

1022 **DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH**
1023 **IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

1024

1025 **HOW SUPPLIED**

1026 **LEVAQUIN Tablets**

1027 LEVAQUIN (levofloxacin tablets) Tablets are supplied as 250-, 500, and
1028 750 mg modified rectangular, film-coated tablets. LEVAQUIN Tablets are
1029 packaged in bottles and in unit-dose blister strips in the following
1030 configurations:

1031

1032 250-mg tablets: color: terra cotta pink
1033 debossing: "LEVAQUIN" on side 1 and "250" on side 2
1034 bottles of 50 (NDC 0045-1520-50)
1035 unit-dose/100 tablets (NDC 0045-1520-10)

1036

1037 500 mg tablets: color: peach
1038 debossing: "LEVAQUIN" on side 1 and "500" on side 2
1039 bottles of 50 (NDC 0045-1525-50)
1040 unit-dose/100 tablets (NDC 0045-1525-10)

1041

1042 750 mg tablets: color: white
1043 debossing: "LEVAQUIN" on side 1 and "750" on side 2
1044 bottles of 50 (NDC 0045-1530-50)
1045 unit-dose/100 tablets (NDC 0045-1530-10)

1046

1047 LEVAQUIN Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed
1048 containers.

1049

1050 LEVAQUIN Tablets are manufactured for OMP DIVISION, ORTHO-McNEIL
1051 PHARMACEUTICAL, INC. by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

1052

1053 **LEVAQUIN Injection**

1054 **Single-Use Vials:** LEVAQUIN (levofloxacin injection) Injection is supplied in
1055 single-use vials. Each vial contains a concentrated solution with the equivalent
1056 of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL
1057 vials.

1058

1059 25 mg/mL, 20 mL vials (NDC 0045-0069-51)
1060 25 mg/mL, 30 mL vials (NDC 0045-0069-55)

1061

1062 LEVAQUIN Injection in Single-Use Vials should be stored at controlled room
1063 temperature and protected from light.

1064

1065 LEVAQUIN Injection in Single-Use Vials is manufactured for OMP DIVISION,
1066 ORTHO-McNEIL PHARMACEUTICAL, INC. by OMJ Pharmaceuticals, Inc.,
1067 San German, Puerto Rico, 00683.

1068

1069 **Premix in Flexible Containers:** LEVAQUIN (levofloxacin injection) Injection is
1070 supplied as a single-use, premixed solution in flexible containers. Each bag
1071 contains a dilute solution with the equivalent of 250, 500, or 750⁵ mg of
1072 levofloxacin, respectively, in 5% Dextrose (D₅W).

1073
1074 5 mg/mL (250 mg), 50 mL flexible container (NDC 0045-0067-01)

1075
1076 5 mg/mL (500 mg), 100 mL flexible container (NDC 0045-0068-01)

1077
1078 5 mg/mL (750 mg), 150 mL flexible container (NDC 0045-0066-01)

1079
1080 LEVAQUIN Injection Premix in Flexible Containers should be stored at or
1081 below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not
1082 adversely affect the product. Avoid excessive heat and protect from freezing
1083 and light.

1084
1085 LEVAQUIN Injection Premix in Flexible Containers is manufactured for OMP
1086 DIVISION, ORTHO-McNEIL PHARMACEUTICAL, INC. by ABBOTT
1087 Laboratories, North Chicago, IL 60064.

1088
1089 **CLINICAL STUDIES**

1090 **Community-Acquired Bacterial Pneumonia**

1091 Adult inpatients and outpatients with a diagnosis of community-acquired
1092 bacterial pneumonia were evaluated in two pivotal clinical studies. In the first
1093 study, 590 patients were enrolled in a prospective, multi-center, unblinded
1094 randomized trial comparing levofloxacin 500 mg once daily orally or
1095 intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or
1096 in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally
1097 twice daily for a total of 7 to 14 days. Patients assigned to treatment with the
1098 control regimen were allowed to receive erythromycin (or doxycycline if
1099 intolerant of erythromycin) if an infection due to atypical pathogens was
1100 suspected or proven. Clinical and microbiologic evaluations were performed
1101 during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy.
1102 Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days
1103 posttherapy, the primary efficacy variable in this study, was superior (95%) to
1104 the control group (83%) [95% CI of -19,-6]. In the second study, 264 patients
1105 were enrolled in a prospective, multi-center, non-comparative trial of 500 mg
1106 levofloxacin administered orally or intravenously once daily for 7 to 14 days.
1107 Clinical success for clinically evaluable patients was 93%. For both studies, the
1108 clinical success rate in patients with atypical pneumonia due to *Chlamydia*
1109 *pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were
1110 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both
1111 studies were as follows:

1112

<u>Pathogen</u>	<u>No. Pathogens</u>	<u>Microbiologic Eradication Rate (%)</u>
<i>H. influenzae</i>	55	98
<i>S. pneumoniae</i>	83	95

<i>S. aureus</i>	17	88
<i>M. catarrhalis</i>	18	94
<i>H. parainfluenzae</i>	19	95
<i>K. pneumoniae</i>	10	100.0

1113

1114 Additional studies were initiated to evaluate the utility of LEVAQUIN in
1115 community-acquired pneumonia due to *S. pneumoniae*, with particular
1116 interest in penicillin-resistant strains (MIC value for penicillin —2 µg/mL). In
1117 addition to the studies previously discussed, inpatients and outpatients with
1118 mild to severe community-acquired pneumonia were evaluated in six
1119 additional clinical studies; one double-blind study, two open label randomized
1120 studies, and three open label non-comparative studies. The total number of
1121 clinically evaluable patients with *S.pneumoniae* across all 8 studies was 250
1122 for levofloxacin and 41 for comparators. The clinical success rate (cured or
1123 improved) among the 250 levofloxacin-treated patients with *S. pneumoniae*
1124 was 245/250 (98%). The clinical success rate among the 41 comparator-
1125 treated patients with *S. pneumoniae* was 39/41 (95%).

1126

1127 Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone
1128 comparator-treated patients with community-acquired pneumonia due to
1129 penicillin-resistant *S. pneumoniae* (MIC value for penicillin —2 µg/mL) were
1130 identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following
1131 the completion of therapy. Fifteen out of the 15 evaluable levofloxacin-treated
1132 patients with community-acquired pneumonia due to penicillin-resistant
1133 *S. pneumoniae* achieved clinical success (cure or improvement). Of these 15
1134 patients, 6 were bacteremic and 5 were classified as having severe disease.
1135 Of the 4 comparator-treated patients with community-acquired pneumonia
1136 due to penicillin-resistant *S. pneumoniae*, 3 were evaluable for clinical
1137 efficacy. Three out of the 3 evaluable comparator-treated patients achieved
1138 clinical success. All three of the comparator-treated patients were bacteremic
1139 and had disease classified as severe.

1140 **Complicated Skin and Skin Structure Infections**

1141 Three hundred ninety-nine patients were enrolled in an open-label,
1142 randomized, comparative study for complicated skin and skin structure
1143 infections. The patients were randomized to receive either levofloxacin
1144 750mg QD (IV followed by oral), or an approved comparator for a median of
1145 10 ± 4.7 days. As is expected in complicated skin and skin structure
1146 infections, surgical procedures were performed in the levofloxacin and
1147 comparator groups. Surgery (incision and drainage or debridement) was
1148 performed on 45% of the levofloxacin treated patients and 44% of the
1149 comparator treated patients, either shortly before or during antibiotic
1150 treatment and formed an integral part of therapy for this indication.

1151

1152 Among those who could be evaluated clinically 2-5 days after completion of
1153 study drug, overall success rates (improved or cured) were 116/138 (84.1%)
1154 for patients treated with levofloxacin and 106/132 (80.3%) for patients treated
1155 with the comparator.

1156

1157 Success rates varied with the type of diagnosis ranging from 68% in patients
1158 with infected ulcers to 90% in patients with infected wounds and abscesses.
1159 These rates were equivalent to those seen with comparator drugs.

1160

1161 **ANIMAL PHARMACOLOGY**

1162 Levofloxacin and other quinolones have been shown to cause arthropathy in
1163 immature animals of most species tested. (See **WARNINGS**.) In immature
1164 dogs (4 - 5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous
1165 doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic
1166 lesions. Administration at oral doses of 300 mg/kg/day for 7 days and
1167 intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in
1168 juvenile rats.

1169

1170 When tested in a mouse ear swelling bioassay, levofloxacin exhibited
1171 phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other
1172 quinolones.

1173

1174 While crystalluria has been observed in some intravenous rat studies, urinary
1175 crystals are not formed in the bladder, being present only after micturition and
1176 are not associated with nephrotoxicity.

1177

1178 In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant
1179 administration of non-steroidal anti-inflammatory drugs.

1180

1181 In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous
1182 injection produced hypotensive effects. These effects were considered to be
1183 related to histamine release.

1184

1185 In vitro and in vivo studies in animals indicate that levofloxacin is neither an
1186 enzyme inducer or inhibitor in the human therapeutic plasma concentration
1187 range; therefore, no drug metabolizing enzyme-related interactions with other
1188 drugs or agents are anticipated.

1189

1190 **REFERENCES**

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1195

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1197 Standards for Antimicrobial Disk Susceptibility Tests Sixth Edition.
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1199 Wayne, PA, January, 1997.

1200

1201

1202 [ADD LOGO]

1203

1204 OMP DIVISION

1205 ORTHO-McNEIL PHARMACEUTICAL, INC.
1206 Raritan, New Jersey, USA 08869
1207 U.S. Patent No. 4,382,892 and U.S. Patent No. 5,053,407.

1208
1209

Patient Information About:

LEVAQUIN[®]

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1211
1212
1213
1214

(levofloxacin tablets)
250 mg Tablets, 500 mg Tablets, and 750 mg Tablets

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1217
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1219
1220
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1222

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.

1223
1224

What is LEVAQUIN[®]?

1225
1226
1227
1228
1229
1230

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.

1231
1232
1233
1234

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

1235
1236
1237
1238
1239

You should contact your health care professional if you think that your condition is not improving while taking LEVAQUIN[®]. LEVAQUIN[®] Tablets are terra cotta pink for the 250 mg tablet, peach colored for the 500 mg tablet, or white for the 750 mg tablet.

1240
1241

How and when should I take LEVAQUIN[®]?

1242
1243
1244
1245
1246

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 and drink fluids liberally.

1247
1248
1249
1250
1251
1252

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.

1253 **Who should not take LEVAQUIN[®]?**
1254

1255 You should not take LEVAQUIN[®] if you have ever had a severe allergic
1256 reaction to any of the group of antibiotics known as “quinolones” such as
1257 ciprofloxacin. Serious and occasionally fatal allergic reactions have been
1258 reported in patients receiving therapy with quinolones, including LEVAQUIN[®].

1259
1260 If you are pregnant or are planning to become pregnant while taking
1261 LEVAQUIN[®], talk to your health care professional before taking this
1262 medication. LEVAQUIN[®] is not recommended for use during pregnancy or
1263 nursing, as the effects on the unborn child or nursing infant are unknown.

1264
1265 LEVAQUIN[®] is not recommended for children.

1266
1267
1268 **What are possible side effects of LEVAQUIN[®]?**

1269
1270 LEVAQUIN[®] is generally well tolerated. The most common side effects
1271 caused by LEVAQUIN[®], which are usually mild, include nausea, diarrhea,
1272 itching, abdominal pain, dizziness, flatulence, rash and vaginitis in women.

1273
1274 You should be careful about driving or operating machinery until you are sure
1275 LEVAQUIN[®] is not causing dizziness.

1276
1277 Allergic reactions have been reported in patients receiving quinolones
1278 including LEVAQUIN[®], even after just one dose. If you develop hives, skin
1279 rash or other symptoms of an allergic reaction, you should stop taking this
1280 medication and call your health care professional.

1281
1282 Ruptures of shoulder, hand, or Achilles tendons have been reported in
1283 patients receiving quinolones, including LEVAQUIN[®]. If you develop pain,
1284 swelling, or rupture of a tendon you should stop taking LEVAQUIN[®] and
1285 contact your health care professional.

1286
1287 Some quinolone antibiotics have been associated with the development of
1288 phototoxicity (“sunburns” and “blistering sunburns”) following exposure to
1289 sunlight or other sources of ultraviolet light such as artificial ultraviolet light
1290 used in tanning salons. LEVAQUIN[®] has been infrequently associated with
1291 phototoxicity. You should avoid excessive exposure to sunlight or artificial
1292 ultraviolet light while you are taking LEVAQUIN[®].

1293
1294 If you have diabetes and you develop a hypoglycemic reaction while on
1295 LEVAQUIN[®], you should stop taking LEVAQUIN[®] and call your health care
1296 professional.

1297

1298 Convulsions have been reported in patients receiving quinolone antibiotics
1299 including LEVAQUIN[®]. If you have experienced convulsions in the past, be
1300 sure to let your physician know that you have a history of convulsions.

1301
1302 Quinolones, including LEVAQUIN[®], may also cause central nervous system
1303 stimulation which may lead to tremors, restlessness, anxiety, lightheadedness,
1304 confusion, hallucinations, paranoia, depression, nightmares, insomnia, and,
1305 rarely, suicidal thoughts or acts.

1306
1307 If you notice any side-effects not mentioned in this leaflet or you have
1308 concerns about the side effects you are experiencing, please inform your
1309 health care professional.

1310
1311 For more complete information regarding levofloxacin, please refer to the full
1312 prescribing information, which may be obtained from your health care
1313 professional, pharmacist, or the Physicians Desk Reference (PDR).

1314
1315
1316 **What about other medicines I am taking?** Taking warfarin (Coumadin[®])
1317 and LEVAQUIN[®] together can further predispose you to the development of
1318 bleeding problems. If you take warfarin, be sure to tell your health care
1319 professional.

1320 Many antacids and multivitamins may interfere with the absorption of
1321 LEVAQUIN[®] and may prevent it from working properly. You should take
1322 LEVAQUIN[®] either 2 hours before or 2 hours after taking these products.

1323
1324 It is important to let your health care professional know all of the medicines
1325 you are using.

1326
1327

1328 **Other information**

1329

1330 Take your dose of LEVAQUIN[®] once a day.

1331

1332 Complete the course of medication even if you are feeling better.

1333

1334 Keep this medication out of the reach of children.

1335

1336 This information does not take the place of discussions with your doctor or
1337 health care professional about your medical condition or your treatment.