

1 **CIPRO® (ciprofloxacin hydrochloride) TABLETS**
2 **CIPRO® (ciprofloxacin) 5% and 10% ORAL SUSPENSION**

3
4 **PZXXXXXX**

8/29/00

5
6 **DESCRIPTION**

7 CIPRO® (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) Oral
8 Suspension are synthetic broad spectrum antimicrobial agents for oral
9 administration. Ciprofloxacin hydrochloride, USP, a fluoroquinolone, is the
10 monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-
11 (1-piperazinyl)-3-quinolinecarboxylic acid. It is a faintly yellowish to light yellow
12 crystalline substance with a molecular weight of 385.8. Its empirical formula is
13 $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and its chemical structure is as follows:

14
15 [STRUCTURE]

16
17 Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-
18 quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular
19 weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its
20 chemical structure is as follows:

21
22 [STRUCTURE]

23
24 Ciprofloxacin differs from other quinolones in that it has a fluorine atom at the 6-
25 position, a piperazine moiety at the 7-position, and a cyclopropyl ring at the 1-
26 position.

27
28 CIPRO® film-coated tablets are available in 100-mg, 250-mg, 500-mg and 750-mg
29 (ciprofloxacin equivalent) strengths. The inactive ingredients are starch,
30 microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate,
31 hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.

32
33 Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and
34 10% (10 g ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a
35 white to slightly yellowish suspension with strawberry flavor which may contain
36 yellow-orange droplets. It is composed of ciprofloxacin microcapsules and diluent
37 which are mixed prior to dispensing (See instructions for USE/HANDLING). The
38 components of the suspension have the following compositions:

39
40 Microcapsules - ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer,
41 hydroxypropyl methylcellulose, magnesium stearate, and Polysorbate 20.
42 Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

43
44
45 **CLINICAL PHARMACOLOGY**

Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations and area under the curve are shown in the chart for the 250-mg to 1000-mg dose range.

Dose (mg)	Maximum Serum Concentration (mg/mL)	Area Under Curve (AUC) (mg·hr/mL)
250	1.2	4.8
500	2.4	11.6
750	4.3	20.2
1000	5.4	30.8

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750-mg are 0.1, 0.2, and 0.4 mg/mL, respectively. Serum concentrations increase proportionately with doses up to 1000-mg.

A 500-mg oral dose given every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours. A 750-mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750-mg oral dose results in a C_{max} similar to that observed with a 400-mg I.V. dose. A 250-mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

**Steady-state Pharmacokinetic Parameter
Following Multiple Oral and I.V. Doses**

Parameters	500 mg q12h, P.O.	400 mg q12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	13.7 ^a	12.7 ^a	31.6 ^b	32.9 ^c
C_{max} ($\mu\text{g/mL}$)	2.97	4.56	3.59	4.07

^aAUC_{0-12h} ^bAUC_{24h}=AUC_{0-12h}x2 ^cAUC_{24h}=AUC_{0-8h}x3

90 The serum elimination half-life in subjects with normal renal function is approximately
91 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the
92 urine as unchanged drug. After a 250-mg oral dose, urine concentrations of
93 ciprofloxacin usually exceed 200 µg/mL during the first two hours and are
94 approximately 30 µg/mL at 8 to 12 hours after dosing. The urinary excretion of
95 ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance
96 of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal
97 glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would
98 seem to play a significant role in its elimination. Co-administration of probenecid
99 with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal
100 clearance and a 50% increase in its concentration in the systemic circulation.
101 Although bile concentrations of ciprofloxacin are several fold higher than serum
102 concentrations after oral dosing, only a small amount of the dose administered is
103 recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is
104 recovered from the bile in the form of metabolites. Approximately 20 to 35% of an
105 oral dose is recovered from the feces within 5 days after dosing. This may arise
106 from either biliary clearance or transintestinal elimination. Four metabolites have
107 been identified in human urine which together account for approximately 15% of an
108 oral dose. The metabolites have antimicrobial activity, but are less active than
109 unchanged ciprofloxacin.

110
111 With oral administration, a 500-mg dose, given as 10 mL of the 5% CIPRO®
112 Suspension (containing 250-mg ciprofloxacin/5mL) is bioequivalent to the 500-mg
113 tablet. A 10 mL volume of the 5% CIPRO® Suspension (containing 250-mg
114 ciprofloxacin/5mL) is bioequivalent to a 5 mL volume of the 10% CIPRO®
115 Suspension (containing 500-mg ciprofloxacin/5mL).

116
117 When CIPRO® Tablet is given concomitantly with food, there is a delay in the
118 absorption of the drug, resulting in peak concentrations that occur closer to 2 hours
119 after dosing rather than 1 hour whereas there is no delay observed when CIPRO®
120 Suspension is given with food. The overall absorption of CIPRO® Tablet or CIPRO®
121 Suspension, however, is not substantially affected. The pharmacokinetics of
122 ciprofloxacin given as the suspension are also not affected by food. Concurrent
123 administration of antacids containing magnesium hydroxide or aluminum hydroxide
124 may reduce the bioavailability of ciprofloxacin by as much as 90%. (See
125 **PRECAUTIONS.**)

126
127 The serum concentrations of ciprofloxacin and metronidazole were not altered when
128 these two drugs were given concomitantly.

129
130 Concomitant administration of ciprofloxacin with theophylline decreases the
131 clearance of theophylline resulting in elevated serum theophylline levels and
132 increased risk of a patient development CNS or other adverse reactions.
133 Ciprofloxacin also decreases caffeine clearance and inhibits the formation of
134 paraxanthine after caffeine administration. (See **PRECAUTIONS.**)

135

136 Pharmacokinetic studies of the oral (single dose) and intravenous (single and
137 multiple dose) forms of ciprofloxacin indicate that plasma concentrations of
138 ciprofloxacin are higher in elderly subjects (>65 years) as compared to young
139 adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is
140 approximately 30%, and can be at least partially attributed to decreased renal
141 clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the
142 elderly. These differences are not considered clinically significant. (See
143 **PRECAUTIONS: Geriatric Use.**)

144

145 In patients with reduced renal function, the half-life of ciprofloxacin is slightly
146 prolonged. Dosage adjustments may be required. (See **DOSAGE AND**
147 **ADMINISTRATION.**)

148

149 In preliminary studies in patients with stable chronic liver cirrhosis, no significant
150 changes in ciprofloxacin pharmacokinetics have been observed. The kinetics of
151 ciprofloxacin in patients with acute hepatic insufficiency, however, have not been
152 fully elucidated.

153

154 The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be
155 high enough to cause significant protein binding interactions with other drugs.

156

157 After oral administration, ciprofloxacin is widely distributed throughout the body.
158 Tissue concentrations often exceed serum concentrations in both men and women,
159 particularly in genital tissue including the prostate. Ciprofloxacin is present in active
160 form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum,
161 skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin
162 has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug
163 diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are
164 generally less than 10% of peak serum concentrations. Low levels of the drug have
165 been detected in the aqueous and vitreous humors of the eye.

166

167 **Microbiology:** Ciprofloxacin has *in vitro* activity against a wide range of gram-
168 negative and gram-positive organisms. The bactericidal action of ciprofloxacin
169 results from interference with the enzyme DNA gyrase which is needed for the
170 synthesis of bacterial DNA. Ciprofloxacin does not cross-react with other
171 antimicrobial agents such as beta-lactams or aminoglycosides; therefore,
172 organisms resistant to these drugs may be susceptible to ciprofloxacin. *In vitro*
173 studies have shown that additive activity often results when ciprofloxacin is
174 combined with other antimicrobial agents such as beta-lactams, aminoglycosides,
175 clindamycin, or metronidazole. Synergy has been reported particularly with the
176 combination of ciprofloxacin and a beta-lactam; antagonism is observed only rarely.

177

178 Ciprofloxacin has been shown to be active against most strains of the following
179 microorganisms, both *in vitro* and in clinical infections as described in the

180 **INDICATIONS AND USAGE** section of the package insert for CIPRO®
181 (ciprofloxacin hydrochloride) Tablets and CIPRO® (ciprofloxacin) 5% and 10% Oral
182 Suspension.

183

184 **Aerobic gram-positive microorganisms**

185 *Enterococcus faecalis* (Many strains are only moderately susceptible.)

186 *Staphylococcus aureus* (methicillin susceptible)

187 *Staphylococcus epidermidis*

188 *Staphylococcus saprophyticus*

189 *Streptococcus pneumoniae*

190 *Streptococcus pyogenes*

191

192

193 **Aerobic gram-negative microorganisms**

194 *Campylobacter jejuni* *Proteus mirabilis*

195 *Citrobacter diversus* *Proteus vulgaris*

196 *Citrobacter freundii* *Providencia rettgeri*

197 *Enterobacter cloacae* *Providencia stuartii*

198 *Escherichia coli* *Pseudomonas aeruginosa*

199 *Haemophilus influenzae* *Salmonella typhi*

200 *Haemophilus parainfluenzae* *Serratia marcescens*

201 *Klebsiella pneumoniae* *Shigella boydii*

202 *Moraxella catarrhalis* *Shigella dysenteriae*

203 *Morganella morganii* *Shigella flexneri*

204 *Neisseria gonorrhoeae* *Shigella sonnei*

205

206

207 Ciprofloxacin has been shown to be active against most strains of the following
208 microorganisms, both *in vitro* and in clinical infections as described in the
209 **INDICATIONS AND USAGE** section of the package insert for CIPRO® I.V.
210 (ciprofloxacin for intravenous infusion).

211

212 **Aerobic gram-positive microorganisms**

213 *Enterococcus faecalis* (Many strains are only moderately susceptible.)

214 *Staphylococcus aureus* (methicillin susceptible)

215 *Staphylococcus epidermidis*

216 *Staphylococcus saprophyticus*

217 *Streptococcus pneumoniae*

218 *Streptococcus pyogenes*

219

220 **Aerobic gram-negative microorganisms**

221 *Citrobacter diversus* *Morganella morganii*

222 *Citrobacter freundii* *Proteus mirabilis*

223	<i>Enterobacter cloacae</i>	<i>Proteus vulgaris</i>
224	<i>Escherichia coli</i>	<i>Providencia rettgeri</i>
225	<i>Haemophilus influenzae</i>	<i>Providencia stuartii</i>
226	<i>Haemophilus parainfluenzae</i>	<i>Pseudomonas aeruginosa</i>
227	<i>Klebsiella pneumoniae</i>	<i>Serratia marcescens</i>

228

229 Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro*
 230 and by use of serum levels as a surrogate marker (see **INDICATIONS AND**
 231 **USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

232

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

235

236 Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL
 237 or less against most (≥90%) strains of the following microorganisms; however, the
 238 safety and effectiveness of ciprofloxacin in treating clinical infections due to these
 239 microorganisms have not been established in adequate and well-controlled clinical
 240 trials.

241

242 **Aerobic gram-positive microorganisms**

243 *Staphylococcus haemolyticus*

244 *Staphylococcus hominis*

245

246 **Aerobic gram-negative microorganisms**

247 *Acinetobacter lwoffii* *Pasteurella multocida*

248 *Aeromonas hydrophila* *Salmonella enteritidis*

249 *Edwardsiella tarda* *Vibrio cholerae*

250 *Enterobacter aerogenes* *Vibrio parahaemolyticus*

251 *Klebsiella oxytoca* *Vibrio vulnificus*

252 *Legionella pneumophila* *Yersinia enterocolitica*

253

254 Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas*
 255 *maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including
 256 *Bacteroides fragilis* and *Clostridium difficile*.

257

258 Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has
 259 little effect when tested *in vitro*. The minimal bactericidal concentration (MBC)
 260 generally does not exceed the minimal inhibitory concentration (MIC) by more than a
 261 factor of 2. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step
 262 mutation).

263

264 **Susceptibility Tests**

265 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial
266 minimum inhibitory concentrations (MICs). These MICs provide estimates of the
267 susceptibility of bacteria to antimicrobial compounds. The MICs should be
268 determined using a standardized procedure. Standardized procedures are based
269 on a dilution method¹ (broth or agar) or equivalent with standardized inoculum
270 concentrations and standardized concentrations of ciprofloxacin powder. The MIC
271 values should be interpreted according to the following criteria:

272

273 For testing aerobic microorganisms other than *Haemophilus influenzae*,
274 *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*^a:

275

<u>MIC (mg/mL)</u>	<u>Interpretation</u>
276 ≤ 1	Susceptible (S)
277 2	Intermediate (I)
278 ≥ 4	Resistant (R)

280

281 ^aThese interpretive standards are applicable only to broth microdilution
282 susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with
283 2-5% lysed horse blood.

284

285 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

286

<u>MIC (mg/mL)</u>	<u>Interpretation</u>
287 ≤ 1	Susceptible (S)

289

290 ^b This interpretive standard is applicable only to broth microdilution susceptibility
291 tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using
292 *Haemophilus* Test Medium¹.

293

294 The current absence of data on resistant strains precludes defining any results other
295 than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible “
296 category should be submitted to a reference laboratory for further testing.

297

298 For testing *Neisseria gonorrhoeae*^c:

299

<u>MIC (mg/mL)</u>	<u>Interpretation</u>
300 ≤ 0.06	Susceptible (S)

302

303 ^c This interpretive standard is applicable only to agar dilution test with GC agar base
304 and 1% defined growth supplement.

305

306 The current absence of data on resistant strains precludes defining any results other
307 than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible”
308 category should be submitted to a reference laboratory for further testing.

309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of “Resistant” indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard ciprofloxacin powder should provide the following MIC values:

<u>Organism</u>		<u>MIC (µg/mL)</u>
<i>E. faecalis</i>	ATCC 29212	0.25-2.0
<i>E. coli</i>	ATCC 25922	0.004-0.015
<i>H. influenzae</i> ^a	ATCC 49247	0.004-0.03
<i>N. gonorrhoeae</i> ^b	ATCC 49226	0.001-0.008
<i>P. aeruginosa</i>	ATCC 27853	0.25-1.0
<i>S. aureus</i>	ATCC 29213	0.12-0.5

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

^b This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar dilution procedure using GC agar base and 1% defined growth supplement.

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure² requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

353 For testing aerobic microorganisms other than *Haemophilus influenzae*,
354 *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*^a:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
357 ≥21	Susceptible (S)
358 16-20	Intermediate (I)
359 ≤15	Resistant (R)

360
361 ^a These zone diameter standards are applicable only to tests performed for
362 streptococci using Mueller-Hinton agar supplemented with 5% sheep blood
363 incubated in 5% CO₂.

364 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

<u>Zone Diameter(mm)</u>	<u>Interpretation</u>
367 21	Susceptible (S)

369
370 ^b This zone diameter standard is applicable only to tests *with Haemophilus*
371 *influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium
372 (HTM)².

373
374 The current absence of data on resistant strains precludes defining any results other
375 than “Susceptible”. Strains yielding zone diameter results suggestive of a
376 “nonsusceptible” category should be submitted to a reference laboratory for further
377 testing.

378 For testing *Neisseria gonorrhoeae*^c:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
381 ≥36	Susceptible (S)

383
384 ^c This zone diameter standard is applicable only to disk diffusion tests with GC agar
385 base and 1% defined growth supplement.

386
387 The current absence of data on resistant strains precludes defining any results other
388 than “Susceptible”. Strains yielding zone diameter results suggestive of a
389 “nonsusceptible” category should be submitted to a reference laboratory for further
390 testing.

391 Interpretation should be as stated above for results using dilution techniques.
392 Interpretation involves correlation of the diameter obtained in the disk test with the
393 MIC for ciprofloxacin.
394

395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-µg ciprofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

<u>Organism</u>		<u>Zone Diameter (mm)</u>
<i>E. coli</i>	ATCC 25922	30-40
<i>H. influenzae</i> ^a	ATCC 49247	34-42
<i>N. gonorrhoeae</i> ^b	ATCC 49226	48-58
<i>P. aeruginosa</i>	ATCC 27853	25-33
<i>S. aureus</i>	ATCC 25923	22-30

^aThese quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)².

^b These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

INDICATIONS AND USAGE

CIPRO[®] is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute Sinusitis caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella catarrhalis*.

Lower Respiratory Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*,

437 *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus*
438 *saprophyticus*, or *Enterococcus faecalis*.

439

440 **Acute Uncomplicated Cystitis in females** caused by *Escherichia coli* or
441 *Staphylococcus saprophyticus*. (See **DOSAGE AND ADMINISTRATION**.)

442

443 **Chronic Bacterial Prostatitis** caused by *Escherichia coli* or *Proteus mirabilis*.

444

445 **Complicated Intra-Abdominal Infections** (used in combination with
446 metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*
447 *mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*. (See **DOSAGE AND**
448 **ADMINISTRATION**.)

449

450 **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella*
451 *pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*,
452 *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*, *Pseudomonas*
453 *aeruginosa*, *Staphylococcus aureus* (methicillin susceptible), *Staphylococcus*
454 *epidermidis*, or *Streptococcus pyogenes*.

455

456 **Bone and Joint Infections** caused by *Enterobacter cloacae*, *Serratia*
457 *marcescens*, or *Pseudomonas aeruginosa*.

458

459 **Infectious Diarrhea** caused by *Escherichia coli* (enterotoxigenic strains),
460 *Campylobacter jejuni*, *Shigella boydii**, *Shigella dysenteriae*, *Shigella Flexneri* or
461 *Shigella sonnei** when antibacterial therapy is indicated.

462

463 **Typhoid Fever (Enteric Fever)** caused by *Salmonella typhi*.

464

465 NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier
466 state has not been demonstrated.

467

468 **Uncomplicated cervical and urethral gonorrhea** due to *Neisseria gonorrhoeae*.

469

470 **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of
471 disease following exposure to aerosolized *Bacillus anthracis*.

472

473 Ciprofloxacin serum concentrations achieved in humans serve as a surrogate
474 endpoint reasonably likely to predict clinical benefit and provide the basis for this
475 indication.⁴ (See also, **INHALATIONAL ANTHRAX – ADDITIONAL**
476 **INFORMATION**).

477

478 *Although treatment of infections due to this organism in this organ system
479 demonstrated a clinically significant outcome, efficacy was studied in fewer than 10
480 patients.

481

482 If anaerobic organisms are suspected of contributing to the infection, appropriate
483 therapy should be administered.

484

485 Appropriate culture and susceptibility tests should be performed before treatment in
486 order to isolate and identify organisms causing infection and to determine their
487 susceptibility to ciprofloxacin. Therapy with CIPRO® may be initiated before results
488 of these tests are known; once results become available appropriate therapy should
489 be continued. As with other drugs, some strains of *Pseudomonas aeruginosa* may
490 develop resistance fairly rapidly during treatment with ciprofloxacin. Culture and
491 susceptibility testing performed periodically during therapy will provide information
492 not only on the therapeutic effect of the antimicrobial agent but also on the possible
493 emergence of bacterial resistance.

494

495 **CONTRAINDICATIONS**

496 CIPRO® (ciprofloxacin hydrochloride) is contraindicated in persons with a history of
497 hypersensitivity to ciprofloxacin or any member of the quinolone class of
498 antimicrobial agents.

499

500 **WARNINGS**

501 **THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC**

502 **PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), -**

503 **EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE),**

504 **PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN**

505 **ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and**

506 **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused

507 lameness in immature dogs. Histopathological examination of the weight-bearing

508 joints of these dogs revealed permanent lesions of the cartilage. Related

509 quinolone-class drugs also produce erosions of cartilage of weight-bearing joints

510 and other signs of arthropathy in immature animals of various species. (See

511 **ANIMAL PHARMACOLOGY.**)

512

513 Convulsions, increased intracranial pressure, and toxic psychosis have been
514 reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may
515 also cause central nervous system (CNS) events including: dizziness, confusion,
516 tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These
517 reactions may occur following the first dose. If these reactions occur in patients
518 receiving ciprofloxacin, the drug should be discontinued and appropriate measures
519 instituted. As with all quinolones, ciprofloxacin should be used with caution in
520 patients with known or suspected CNS disorders that may predispose to seizures
521 or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in

522 the presence of other risk factors that may predispose to seizures or lower the
523 seizure threshold (e.g. certain drug therapy, renal dysfunction). (See
524 **PRECAUTIONS: General, Information for Patients, Drug Interactions and**
525 **ADVERSE REACTIONS.**)

526
527 **SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS**
528 **RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND**
529 **THEOPHYLLINE.** These reactions have included cardiac arrest, seizure, status
530 epilepticus, and respiratory failure. Although similar serious adverse effects have
531 been reported in patients receiving theophylline alone, the possibility that these
532 reactions may be potentiated by ciprofloxacin cannot be eliminated. If concomitant
533 use cannot be avoided, serum levels of theophylline should be monitored and
534 dosage adjustments made as appropriate.

535
536 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some
537 following the first dose, have been reported in patients receiving quinolone therapy.
538 Some reactions were accompanied by cardiovascular collapse, loss of
539 consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching.
540 Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic
541 reactions require immediate emergency treatment with epinephrine. Oxygen,
542 intravenous steroids, and airway management, including intubation, should be
543 administered as indicated.

544
545 Severe hypersensitivity reactions characterized by rash, fever, eosinophilia,
546 jaundice, and hepatic necrosis with fatal outcome have also been rarely reported in
547 patients receiving ciprofloxacin along with other drugs. The possibility that these
548 reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be
549 discontinued at the first appearance of a skin rash or any other sign of
550 hypersensitivity.

551
552 **Pseudomembranous colitis has been reported with nearly all antibacterial**
553 **agents, including ciprofloxacin, and may range in severity from mild to life-**
554 **threatening. Therefore, it is important to consider this diagnosis in patients**
555 **who present with diarrhea subsequent to the administration of antibacterial**
556 **agents.**

557
558 Treatment with antibacterial agents alters the normal flora of the colon and may
559 permit overgrowth of clostridia. Studies indicate that a toxin produced by
560 *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

561
562 After the diagnosis of pseudomembranous colitis has been established, therapeutic
563 measures should be initiated. Mild cases of pseudomembranous colitis usually
564 respond to drug discontinuation alone. In moderate to severe cases, consideration
565 should be given to management with fluids and electrolytes, protein

566 supplementation, and treatment with an antibacterial drug clinically effective against
567 *C. difficile* colitis.

568

569 Achilles and other tendon ruptures that required surgical repair or resulted in
570 prolonged disability have been reported with ciprofloxacin and other quinolones.
571 Ciprofloxacin should be discontinued if the patient experiences pain, inflammation,
572 or rupture of a tendon.

573

574 Ciprofloxacin has not been shown to be effective in the treatment of syphilis.
575 Antimicrobial agents used in high dose for short periods of time to treat gonorrhea
576 may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea
577 should have a serologic test for syphilis at the time of diagnosis. Patients treated
578 with ciprofloxacin should have a follow-up serologic test for syphilis after three
579 months.

580

581

PRECAUTIONS

582 **General:** Crystals of ciprofloxacin have been observed rarely in the urine of human
583 subjects but more frequently in the urine of laboratory animals, which is usually
584 alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin
585 has been reported only rarely in humans because human urine is usually acidic.
586 Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients
587 should be well hydrated to prevent the formation of highly concentrated urine.

588

589 Quinolones, including ciprofloxacin, may also cause central nervous system (CNS)
590 events, including: nervousness, agitation, insomnia, anxiety, nightmares or
591 paranoia. (See **WARNINGS, Information for Patients, and Drug Interactions**.)

592

593 Alteration of the dosage regimen is necessary for patients with impairment of renal
594 function. (See **DOSAGE AND ADMINISTRATION**.)

595

596 Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction
597 has been observed in patients who are exposed to direct sunlight while receiving
598 some members of the quinolone class of drugs. Excessive sunlight should be
599 avoided. Therapy should be discontinued if phototoxicity occurs.

600

601 As with any potent drug, periodic assessment of organ system functions, including
602 renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

603

Information for Patients:

604 Patients should be advised:

- 606 ♦ that ciprofloxacin may be taken with or without meals and to drink fluids liberally.
607 As with other quinolones, concurrent administration of ciprofloxacin with
608 magnesium/aluminum antacids, or sucralfate, Videx® (didanosine)
609 chewable/buffered tablets or pediatric powder, or with other products containing
610 calcium, iron or zinc should be avoided. These products may be taken two

611 hours after or six hours before ciprofloxacin. Ciprofloxacin should not be taken
612 concurrently with milk or yogurt alone, since absorption of ciprofloxacin may be
613 significantly reduced. Dietary calcium as part of a meal, however, does not
614 significantly affect ciprofloxacin absorption

615

616 ◆ that ciprofloxacin may be associated with hypersensitivity reactions, even
617 following a single dose, and to discontinue the drug at the first sign of a skin rash
618 or other allergic reaction.

619

620 ◆ to avoid excessive sunlight or artificial ultraviolet light while receiving
621 ciprofloxacin and to discontinue therapy if phototoxicity occurs.

622

623 ◆ to discontinue treatment; rest and refrain from exercise; and inform their
624 physician if they experience pain, inflammation, or rupture of a tendon.

625

626 ◆ that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients
627 should know how they react to this drug before they operate an automobile or
628 machinery or engage in activities requiring mental alertness or coordination.

629

630 ◆ that ciprofloxacin may increase the effects of theophylline and caffeine. There is
631 a possibility of caffeine accumulation when products containing caffeine are
632 consumed while taking quinolones.

633

634 ◆ that convulsions have been reported in patients receiving quinolones, including
635 ciprofloxacin, and to notify their physician before taking this drug if there is a
636 history of this condition.

637

638 **Drug Interactions:** As with some other quinolones, concurrent administration of
639 ciprofloxacin with theophylline may lead to elevated serum concentrations of
640 theophylline and prolongation of its elimination half-life. This may result in increased
641 risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant
642 use cannot be avoided, serum levels of theophylline should be monitored and
643 dosage adjustments made as appropriate.

644

645 Some quinolones, including ciprofloxacin, have also been shown to interfere with the
646 metabolism of caffeine. This may lead to reduced clearance of caffeine and a
647 prolongation of its serum half-life.

648

649 Concurrent administration of a quinolone, including ciprofloxacin, with multivalent
650 cation-containing products such as magnesium/aluminum antacids, sucralfate,
651 Videx® (didanosine) chewable/buffered tablets or pediatric powder, or products
652 containing calcium, iron, or zinc may substantially decrease its absorption, resulting
653 in serum and urine levels considerably lower than desired. (See **DOSAGE AND**
654 **ADMINISTRATION** for concurrent administration of these agents with ciprofloxacin.)

655

656 Histamine H₂-receptor antagonists appear to have no significant effect on the
657 bioavailability of ciprofloxacin.

658
659 Altered serum levels of phenytoin (increased and decreased) have been reported in
660 patients receiving concomitant ciprofloxacin.

661
662 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has,
663 on rare occasions, resulted in severe hypoglycemia.

664
665 Some quinolones, including ciprofloxacin, have been associated with transient
666 elevations in serum creatinine in patients receiving cyclosporine concomitantly.

667
668 Quinolones have been reported to enhance the effects of the oral anticoagulant
669 warfarin or its derivatives. When these products are administered concomitantly,
670 prothrombin time or other suitable coagulation tests should be closely monitored.

671
672 Probenecid interferes with renal tubular secretion of ciprofloxacin and produces
673 an increase in the level of ciprofloxacin in the serum. This should be considered
674 if patients are receiving both drugs concomitantly.

675
676 As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin
677 may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the
678 patient's condition and microbial susceptibility testing is essential. If superinfection
679 occurs during therapy, appropriate measures should be taken.

680
681 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Eight *in vitro*
682 mutagenicity tests have been conducted with ciprofloxacin, and the test results are
683 listed below:

684
685 Salmonella/Microsome Test (Negative)
686 *E. coli* DNA Repair Assay (Negative)
687 Mouse Lymphoma Cell Forward Mutation Assay (Positive)
688 Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
689 Syrian Hamster Embryo Cell Transformation Assay (Negative)
690 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
691 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion
692 Assay (Negative)
693 Rat Hepatocyte DNA Repair Assay (Positive)

694
695 Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems
696 gave negative results:

697
698 Rat Hepatocyte DNA Repair Assay
699 Micronucleus Test (Mice)

Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.³

In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the highest recommended human dose of 1200 mg based upon body surface area) revealed no evidence of impairment.

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

Nursing Mothers: Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

744 **Pediatric Use:** Safety and effectiveness in pediatric patients and adolescents less
745 than 18 years of age have not been established, except for use in inhalational
746 anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See
747 **WARNINGS**.)

748
749 For the indication of inhalational anthrax (post-exposure), the risk-benefit
750 assessment indicates that administration of ciprofloxacin to pediatric patients is
751 appropriate. For information regarding pediatric dosing in inhalational anthrax
752 (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL**
753 **ANTHRAX – ADDITIONAL INFORMATION**.

754
755 Short-term safety data from a single trial in pediatric cystic fibrosis patients are
756 available. In a randomized, double-blind clinical trial for the treatment of acute
757 pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients
758 received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by
759 ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62
760 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and
761 tobramycin I.V. 3 mg/kg/dose q8h for a total of 10 - 21 days. Patients less than 5
762 years of age were not studied. Safety monitoring in the study included periodic
763 range of motion examinations and gait assessments by treatment-blinded
764 examiners. Patients were followed for an average of 23 days after completing
765 treatment (range 0-93 days). This study was not designed to determine long term
766 effects and the safety of repeated exposure to ciprofloxacin.

767
768 In the study, injection site reactions were more common in the ciprofloxacin group
769 (24%) than in the comparison group (8%). Other adverse events were similar in
770 nature and frequency between treatment arms. Musculoskeletal adverse events
771 were reported in 22% of the patients in the ciprofloxacin group and 21% in the
772 comparison group. Decreased range of motion was reported in 12% of the
773 subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia
774 was reported in 10% of the patients in the ciprofloxacin group and 11% in the
775 comparison group. One of sixty-seven patients developed arthritis of the knee nine
776 days after a ten day course of treatment with ciprofloxacin. Clinical symptoms
777 resolved, but an MRI showed knee effusion without other abnormalities eight months
778 after treatment. However, the relationship of this event to the patient's course of
779 ciprofloxacin can not be definitively determined, particularly since patients with
780 cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease
781 process.

782
783 **Geriatric Use :** In a retrospective analysis of 23 multiple-dose controlled clinical
784 trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25%
785 of patients were greater than or equal to 65 years of age and 10% were greater
786 than or equal to 75 years of age. No overall differences in safety or effectiveness
787 were observed between these subjects and younger subjects, and other reported
788 clinical experience has not identified differences in responses between the elderly

789 and younger patients, but greater sensitivity of some older individuals on any drug
790 therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by
791 the kidney, and the risk of adverse reactions may be greater in patients with
792 impaired renal function. No alteration of dosage is necessary for patients greater
793 than 65 years of age with normal renal function. However, since some older
794 individuals experience reduced renal function by virtue of their advanced age, care
795 should be taken in dose selection for elderly patients, and renal function monitoring
796 may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and
797 **DOSAGE AND ADMINISTRATION**.)

798 **ADVERSE REACTIONS**

800 During clinical investigation with the tablet, 2,799 patients received 2,868 courses
801 of the drug. Adverse events that were considered likely to be drug related occurred
802 in 7.3% of patients treated, possibly related in 9.2% (total of 16.5% thought to be
803 possibly or probably related to drug therapy), and remotely related in 3.0%.
804 Ciprofloxacin was discontinued because of an adverse event in 3.5% of patients
805 treated, primarily involving the gastrointestinal system (1.5%), skin (0.6%), and
806 central nervous system (0.4%).

807
808 The most frequently reported events, drug related or not, were nausea (5.2%),
809 diarrhea (2.3%), vomiting (2.0%), abdominal pain/discomfort (1.7%), headache
810 (1.2%), restlessness (1.1%), and rash (1.1%).

811
812 Additional events that occurred in less than 1% of ciprofloxacin patients are listed
813 below.

814
815 **CARDIOVASCULAR:** palpitation, atrial flutter, ventricular ectopy, syncope,
816 hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest,
817 cerebral thrombosis

818 **CENTRAL NERVOUS SYSTEM:** dizziness, lightheadedness, insomnia,
819 nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive
820 seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia,
821 depersonalization, depression, paresthesia (See above.) (See

822 **PRECAUTIONS.**)

823 **GASTROINTESTINAL:** painful oral mucosa, oral candidiasis, dysphagia,
824 intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic
825 jaundice has been reported.

826 **MUSCULOSKELETAL:** arthralgia or back pain, joint stiffness, achiness, neck or
827 chest pain, flare up of gout

828 **RENAL/UROGENITAL:** interstitial nephritis, nephritis, renal failure, polyuria,
829 urinary retention, urethral bleeding, vaginitis, acidosis

830 **RESPIRATORY:** dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough,
831 hemoptysis, bronchospasm, pulmonary embolism

832 **SKIN/HYPERSENSITIVITY:** pruritus, urticaria, photosensitivity, flushing, fever,
833 chills, angioedema, edema of the face, neck, lips, conjunctivae or hands,

834 cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)
835 Allergic reactions ranging from urticaria to anaphylactic reactions have been
836 reported. (See **WARNINGS**.)

837 **SPECIAL SENSES:** blurred vision, disturbed vision (change in color
838 perception, overbrightness of lights), decreased visual acuity, diplopia, eye
839 pain, tinnitus, hearing loss, bad taste

840
841 Most of the adverse events reported were described as only mild or moderate in
842 severity, abated soon after the drug was discontinued, and required no treatment.

843
844 In several instances nausea, vomiting, tremor, irritability, or palpitation were judged
845 by investigators to be related to elevated serum levels of theophylline possibly as a
846 result of drug interaction with ciprofloxacin.

847
848 In domestic clinical trials involving 214 patients receiving a single 250-mg oral dose,
849 approximately 5% of patients reported adverse experiences without reference to
850 drug relationship. The most common adverse experiences were vaginitis (2%),
851 headache (1%), and vaginal pruritus (1%). Additional reactions, occurring in 0.3%-
852 1% of patients, were abdominal discomfort, lymphadenopathy, foot pain, dizziness,
853 and breast pain. Less than 20% of these patients had laboratory values obtained,
854 and these results were generally consistent with the pattern noted for multi-dose
855 therapy.

856
857 In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets
858 (500 mg BID) to cefuroxime axetil (250 mg - 500 mg BID) and to clarithromycin (500
859 mg BID) in patients with respiratory tract infections, ciprofloxacin demonstrated a
860 CNS adverse event profile comparable to the control drugs.

861
862 **Post-Marketing Adverse Events:** Additional adverse events, regardless of
863 relationship to drug, reported from worldwide marketing experience with quinolones,
864 including ciprofloxacin, are:

865 **BODY AS A WHOLE:** change in serum phenytoin

866 **CARDIOVASCULAR:** postural hypotension, vasculitis

867 **CENTRAL NERVOUS SYSTEM:** agitation, confusion, delirium, dysphasia,
868 myoclonus, nystagmus, toxic psychosis

869 **GASTROINTESTINAL:** constipation, dyspepsia, flatulence, hepatic necrosis,
870 jaundice, pancreatitis, pseudomembranous colitis (The onset of
871 pseudomembranous colitis symptoms may occur during or after antimicrobial
872 treatment.)

873 **HEMIC/LYMPHATIC:** agranulocytosis, hemolytic anemia, methemoglobinemia,
874 prolongation of prothrombin time

875 **METABOLIC/NUTRITIONAL:** elevation of serum triglycerides, cholesterol,
876 blood glucose, serum potassium

877 **MUSCULOSKELETAL:** myalgia, possible exacerbation of myasthenia gravis,
878 tendinitis/tendon rupture

879 RENAL/UROGENITAL: albuminuria, candiduria, renal calculi, vaginal
880 candidiasis
881 SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema
882 multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal
883 necrolysis
884 SPECIAL SENSES: anosmia, taste loss (See **PRECAUTIONS.**)
885

886 **Adverse Laboratory Changes:** Changes in laboratory parameters listed as
887 adverse events without regard to drug relationship are listed below:
888

889 Hepatic - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%),
890 alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin
891 (0.3%).
892 Hematologic - Eosinophilia (0.6%), leukopenia (0.4%), decreased blood
893 platelets (0.1%), elevated blood platelets (0.1%),
894 pancytopenia (0.1%).
895 Renal - Elevations of serum creatinine (1.1%), BUN (0.9%),
896 **CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE**
897 **BEEN REPORTED.**
898

899 Other changes occurring in less than 0.1% of courses were: elevation of serum
900 gammaglutamyl transferase, elevation of serum amylase, reduction in blood
901 glucose, elevated uric acid, decrease in hemoglobin, anemia, bleeding diathesis,
902 increase in blood monocytes, leukocytosis.
903

904 **OVERDOSAGE**

905 In the event of acute overdosage, the stomach should be emptied by inducing
906 vomiting or by gastric lavage. The patient should be carefully observed and given
907 supportive treatment. Adequate hydration must be maintained. Only a small
908 amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or
909 peritoneal dialysis.
910

911 In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions
912 was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.
913

914 Single doses of ciprofloxacin were relatively non-toxic via the oral route of
915 administration in mice, rats, and dogs. No deaths occurred within a 14-day post
916 treatment observation period at the highest oral doses tested; up to 5000 mg/kg in
917 either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed
918 included hypoactivity and cyanosis in both rodent species and severe vomiting in
919 dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin > 2500
920 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.
921

922 **DOSAGE AND ADMINISTRATION**

923
924 The recommended adult dosage for acute sinusitis is 500-mg every 12 hours.

925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958

Lower respiratory tract infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

Severe/complicated urinary tract infections or urinary tract infections caused by organisms not highly susceptible to ciprofloxacin may be treated with 500-mg every 12 hours. For other mild/moderate urinary infections, the usual adult dosage is 250-mg every 12 hours.

In acute uncomplicated cystitis in females, the usual dosage is 100-mg or 250-mg every 12 hours. For acute uncomplicated cystitis in females, 3 days of treatment is recommended while 7 to 14 days is suggested for other mild/moderate, severe or complicated urinary tract infections.

The recommended adult dosage for chronic bacterial prostatitis is 500-mg every 12 hours.

The recommended adult dosage for oral sequential therapy of complicated intra-abdominal infections is 500-mg every 12 hours. (To provide appropriate anaerobic activity, metronidazole should be given according to product labeling.) (See CIPRO® I.V. package insert.)

Skin and skin structure infections and bone and joint infections may be treated with 500-mg every 12 hours. For more severe or complicated infections, a dosage of 750-mg may be given every 12 hours.

The recommended adult dosage for infectious diarrhea or typhoid fever is 500-mg every 12 hours. For the treatment of uncomplicated urethral and cervical gonococcal infections, a single 250-mg dose is recommended.

See Instructions To The Pharmacist for Use/Handling of CIPRO® Oral Suspension.

<u>DOSAGE GUIDELINES</u>				
<u>Infection Durations†</u>	<u>Type or Severity</u>	<u>Unit Dose</u>	<u>Frequency</u>	<u>Usual</u>
Acute Sinusitis	Mild/Moderate	500-mg	q 12 h	10 days
Lower Respiratory Tract	Mild/Moderate	500-mg	q 12 h	7 to 14 days
	Severe/Complicated	750-mg	q 12 h	7 to 14 days
Urinary Tract	Acute Uncomplicated	100-mg or 250-mg	q 12 h	3 Days
	Mild/Moderate	250-mg	q 12 h	7 to 14 Days
	Severe/Complicated	500-mg	q 12 h	7 to 14 Days

Chronic Bacterial	Mild/Moderate	500-mg	q 12 h	28 Days
Prostatitis				
Intra-Abdominal*	Complicated	500-mg	q 12 h	7 to 14 Days
Skin and Skin Structure	Mild/Moderate	500-mg	q 12 h	7 to 14 Days
	Severe/Complicated	750-mg	q 12 h	7 to 14 Days
Bone and Joint	Mild/Moderate	500-mg	q 12 h	≥ 4 to 6 weeks
	Severe/Complicated	750-mg	q 12 h	≥ 4 to 6 weeks
Infectious Diarrhea	Mild/Moderate/Severe	500-mg	q 12 h	5 to 7 Days
Typhoid Fever	Mild/Moderate	500-mg	q 12 h	10 Days
Urethral and Cervical Gonococcal Infections	Uncomplicated	250-mg	single dose	single dose
Inhalational anthrax (post-exposure)**	Adult	500-mg	q 12 h	60 Days
	Pediatric	15 mg/kg per dose, not to exceed 500-mg per dose	q 12 h	60 Days

959 * used in conjunction with metronidazole

960 † Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of
961 infection have disappeared, except for inhalational anthrax (post-exposure).

962 ** Drug administration should begin as soon as possible after suspected or confirmed exposure.
963 This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in
964 humans, reasonably likely to predict clinical benefit.⁴ For a discussion of ciprofloxacin serum
965 concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL**
966 **INFORMATION.**

967

968 One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250-mg of
969 ciprofloxacin.

970 One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500-mg of
971 ciprofloxacin.

972 See Instructions for USE/HANDLING.

973

974 Volume (mL) of Oral Suspension

<u>Dosage</u>	<u>5%</u>	<u>10%</u>
975 250-mg	5 mL	2.5 mL
976 500-mg	10 mL	5 mL
977 750-mg	15 mL	7.5 mL

979

980 **CIPRO (ciprofloxacin) 5% and 10% Oral Suspension should not be**
981 **administered through feeding tubes due to its physical characteristics.**

982

983 **Complicated Intra-Abdominal Infections:** Sequential therapy [parenteral to oral -
984 400-mg CIPRO[®] IV q 12 h (plus IV metronidazole) → 500-mg CIPRO[®] Tablets q
985 12 h (plus oral metronidazole)] can be instituted at the discretion of the physician.

986

987 The determination of dosage for any particular patient must take into consideration
988 the severity and nature of the infection, the susceptibility of the causative organism,
989 the integrity of the patient's host-defense mechanisms, and the status of renal
990 function and hepatic function.

991
992 The duration of treatment depends upon the severity of infection. Generally
993 ciprofloxacin should be continued for at least 2 days after the signs and symptoms
994 of infection have disappeared. The usual duration is 7 to 14 days; however, for
995 severe and complicated infections more prolonged therapy may be required. Bone
996 and joint infections may require treatment for 4 to 6 weeks or longer. Chronic
997 Bacterial Prostatitis should be treated for 28 days. Infectious diarrhea may be
998 treated for 5-7 days. Typhoid fever should be treated for 10 days.

999
1000 Ciprofloxacin should be administered at least 2 hours before or 6 hours after
1001 magnesium/aluminum antacids, or sucralfate, Videx (Didanoside) chewable /
1002 buffered tablets or pediatric powder for oral solution, or other products containg
1003 calcium, iron or zinc.

1004
1005 **Impaired Renal Function:** Ciprofloxacin is eliminated primarily by renal excretion;
1006 however, the drug is also metabolized and partially cleared through the biliary
1007 system of the liver and through the intestine. These alternate pathways of drug
1008 elimination appear to compensate for the reduced renal excretion in patients with
1009 renal impairment. Nonetheless, some modification of dosage is recommended,
1010 particularly for patients with severe renal dysfunction. The following table provides
1011 dosage guidelines for use in patients with renal impairment; however, monitoring of
1012 serum drug levels provides the most reliable basis for dosage adjustment:

1013
1014 **RECOMMENDED STARTING AND MAINTENANCE DOSES**
1015 **FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

1016
1017

Creatinine Clearance (mL/min)	Dose
>50	See Usual Dosage.
30 - 50	250-500 mg q 12 h
5 - 29	250-500 mg q 18 h
Patients on hemodialysis or Peritoneal dialysis)	250-500 mg q 24 h (after dialysis)

1021
1022
1023

1024 When only the serum creatinine concentration is known, the following formula may
1025 be used to estimate creatinine clearance.

1026
1027 Men: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$
1028

1029
1030 Women: 0.85 x the value calculated for men.

1031 The serum creatinine should represent a steady state of renal function.

1032

1033 In patients with severe infections and severe renal impairment, a unit dose of 750-
1034 mg may be administered at the intervals noted above; however, patients should be
1035 carefully monitored and the serum ciprofloxacin concentration should be measured
1036 periodically. Peak concentrations (1-2 hours after dosing) should generally range
1037 from 2 to 4 µg/mL.

1038

1039 For patients with changing renal function or for patients with renal impairment and
1040 hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will
1041 provide additional guidance for adjusting dosage.

1042

1043

HOW SUPPLIED

1044 CIPRO® (ciprofloxacin hydrochloride) Tablets are available as round, slightly
1045 yellowish film-coated tablets containing 100-mg or 250-mg ciprofloxacin. The 100-
1046 mg tablet is coded with the word "CIPRO" on one side and "100" on the reverse
1047 side. The 250-mg tablet is coded with the word "CIPRO" on one side and "250" on
1048 the reverse side. CIPRO® is also available as capsule shaped, slightly yellowish
1049 film-coated tablets containing 500-mg or 750-mg ciprofloxacin. The 500-mg tablet
1050 is coded with the word "CIPRO" on one side and "500" on the reverse side. The
1051 750-mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse
1052 side. CIPRO® 250-mg, 500-mg, and 750-mg are available in bottles of 50, 100,
1053 and Unit Dose packages of 100. The 100-mg strength is available only as CIPRO®
1054 Cystitis pack containing 6 tablets for use only in female patients with acute
1055 uncomplicated cystitis.

1056

1057

	Strength	NDC Code	Tablet Identification
--	-----------------	-----------------	------------------------------

1058

Bottles of 50:	750-mg	NDC 0026-8514-50	CIPRO 750
----------------	--------	------------------	-----------

Bottles of 100:	250-mg	NDC 0026-8512-51	CIPRO 250
-----------------	--------	------------------	-----------

	500-mg	NDC 0026-8513-51	CIPRO 500
--	--------	------------------	-----------

1062

1063 Unit Dose

Package of 100:	250-mg	NDC 0026-8512-48	CIPRO 250
-----------------	--------	------------------	-----------

	500-mg	NDC 0026-8513-48	CIPRO 500
--	--------	------------------	-----------

	750-mg	NDC 0026-8514-48	CIPRO 750
--	--------	------------------	-----------

1067

1068 Cystitis

Package of 6:	100-mg	NDC 0026-8511-06	CIPRO 100
---------------	--------	------------------	-----------

1070

1071 **Store below 30° C (86° F).**

1072

1073 CIPRO® Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10%
1074 (10g ciprofloxacin in 100 mL) strengths. The drug product is composed of two
1075 components (microcapsules and diluent) which are mixed prior to dispensing. See
1076 Instructions To The Pharmacist For Use/Handling.

1077
1078
1079
1080
1081
1082
1083
1084
1085
1086
1087
1088
1089
1090
1091
1092
1093
1094
1095
1096
1097
1098
1099
1100
1101
1102
1103
1104
1105
1106
1107
1108
1109
1110
1111
1112
1113
1114
1115
1116
1117
1118
1119
1120

Total volume after reconstitution	Ciprofloxacin contents after reconstitution	Ciprofloxacin contents per bottle	NDC Code
100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
100 mL	500 mg/5 mL	10,000 mg	0026-8553-36

Microcapsules and diluent should be stored below 25° C (77° F) and protected from freezing.

Reconstituted product may be stored below 30° C (86° F). Protect from freezing. A teaspoon is provided for the patient.

ANIMAL PHARMACOLOGY

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study in beagles, removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy has been noted after single oral doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

In dogs, ciprofloxacin at 3 and 10 mg/kg by rapid IV injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid IV injection also produces hypotension but the effect in this species is inconsistent and less pronounced.

In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS stimulatory effect of quinolones.

Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

1121

1122

1123

CLINICAL STUDIES
Acute Sinusitis Studies

1124

1125

1126

1127

1128

1129

1130

1131

1132

1133

Ciprofloxacin tablets (500-mg BID) were evaluated for the treatment of acute sinusitis in two randomized, double-blind, controlled clinical trials conducted in the United States. Study 1 compared ciprofloxacin with cefuroxime axetil (250-mg BID) and enrolled 501 patients (400 of whom were valid for the primary efficacy analysis). Study 2 compared ciprofloxacin with clarithromycin (500-mg BID) and enrolled 560 patients (418 of whom were valid for the primary efficacy analysis). The primary test of cure endpoint was a follow-up visit performed approximately 30 days after the completion of treatment with study medication. Clinical response data from these studies are summarized below:

1134

1135

Drug Regimen	Clinical Response Resolution at 30 Day Follow-up n(%)
<u>STUDY 1</u>	
CIPRO 500-mg BID x 10 days	152/197 (77)
Cefuroxime Axetil 250-mg BID x 10 days	145/203 (71)
<u>STUDY 2</u>	
CIPRO 500-mg BID x 10 days	168/212 (79)
Clarithromycin 500-mg BID x 14 days	169/206 (82)

1136

1137

1138

1139

1140

1141

1142

1143

1144

1145

1146

1147

1148

1149

1150

1151

1152

1153

1154

1155

1156

In ciprofloxacin-treated patients enrolled in controlled and uncontrolled acute sinusitis studies, all of which included antral puncture, bacteriological eradication/presumed eradication was documented at the 30 day follow-up visit in 44 of 50 (88%) *H. influenzae*, 17 of 21 (80.9%) *M. catarrhalis*, and 42 of 51 (82.3%) *S. pneumoniae*. Patients infected with *S. pneumoniae* strains whose baseline susceptibilities were intermediate or resistant to ciprofloxacin had a lower success rate than patients infected with susceptible strains.

1157

Uncomplicated Cystitis Studies

1158

1159

1160

1161

1162

1163

1164

1165

1166

1167

1168

Efficacy: Two U.S. double-blind, controlled clinical studies of acute uncomplicated cystitis in women compared ciprofloxacin 100-mg BID for 3 days to ciprofloxacin 250-mg BID for 7 days or control drug. In these two studies, using strict evaluability criteria and microbiologic and clinical response criteria at the 5-9 day post-therapy follow-up, the following clinical resolution and bacterial eradication rates were obtained:

Drug Regimen	Clinical Response Resolution n(%)	Bacteriological Response By Organism (Eradication Rate)	
		<i>E. coli</i> n(%)	<i>S. saprophyticus</i> n(%)

1169

1170

STUDY 1

1171 CIPRO 100-mg

1172 BID x 3 days 82/94 (87) 64/70 (91) 8/8 (100)

1173

1174 CIPRO 250-mg

1175 BID x 7 days 81/86 (94) 67/69 (97) 4/4 (100)

1176

STUDY 2

1177 CIPRO 100-mg

1178 BID x 3 days 134/141 (95) 117/123 (95) 8/8 (100)

1179

1180 Control
1181 (3 days)

128/133 (96) 103/105 (98) 10/10 (100)

1182

INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

1183

1184

1185 The mean serum concentrations of ciprofloxacin associated with a statistically
1186 significant improvement in survival in the rhesus monkey model of inhalational
1187 anthrax are reached or exceeded in adult and pediatric patients receiving oral and
1188 intravenous regimens. (See **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin
1189 pharmacokinetics have been evaluated in various human populations. The mean
1190 peak serum concentration achieved at steady state in human adults receiving 500
1191 mg orally every 12 hours is 2.97 µg/ml, and 4.56 µg/ml following 400 mg
1192 intravenously every 12 hours. The mean trough serum concentration at steady state
1193 for both of these regimens is 0.2 µg/ml. In a study of 10 pediatric patients between 6
1194 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL
1195 and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute
1196 intravenous infusions of 10 mg/kg administered 12 hours apart. After the second
1197 intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a
1198 mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety
1199 data, including effects on cartilage, following the administration of ciprofloxacin to
1200 pediatric patients are limited. (For additional information, see **PRECAUTIONS**,
1201 **Pediatric Use**.) Ciprofloxacin serum concentrations achieved in humans serve as a
1202 surrogate endpoint reasonably likely to predict clinical benefit and provide the basis
1203 for this indication.⁴

1204

1205 A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean
1206 dose of 11 LD₅₀ (~5.5 x 10⁵) spores (range 5-30 LD₅₀) of *B. anthracis* was
1207 conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the
1208 anthrax strain used in this study was 0.08 µg/ml. In the animals studied, mean serum
1209 concentrations of ciprofloxacin achieved at expected T_{max}
1210 (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69
1211 µg/ml. Mean steady state trough concentrations at 12 hours post-dose ranged from
1212 0.12 to 0.19 µg/ml.⁵ Mortality due to anthrax for animals that received a 30-day
1213 regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly
1214 lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one

1215 ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug
1216 administration period.⁶

1217

1218 **Instructions To The Pharmacist For Use/Handling Of CIPRO® Oral**
1219 **Suspension:**

1220

1221 **Preparation of the suspension:**

1222

1223

1224 [IMAGE] 1. The small bottle contains the microcapsules; the
1225 large bottle contains the diluent.

1226

1227

1228 [IMAGE] 2. Open both bottles. Child-proof cap: Press down
1229 according to instructions on the cap while turning to the
1230 left.

1231

1232 [IMAGE] 3. Pour the microcapsules completely into the large
1233 bottle of diluent. **Do not add water to the**
1234 **suspension.**

1235

1236 4. Remove the top layer of the diluent bottle label (to
1237 reveal the CIPRO® Oral Suspension label).

1238

1239 [IMAGE] 5. Close the large bottle completely according to
1240 the directions on the cap and shake vigorously for
1241 about 15 seconds. The suspension is ready for use.

1242

1243 **Instructions To The Patient For Taking CIPRO® Oral Suspension:**

1244

1245 **Shake vigorously each time before use for approximately 15 seconds.**

1246

1247 Swallow the prescribed amount of suspension. Do not chew the microcapsules.
1248 Reclose the bottle completely after use according to the instructions on the cap.
1249 Shake vigorously each time before use for approximately 15 seconds. The product
1250 can be used for 14 days when stored in a refrigerator or at room temperature
1251 (below 86°F). After treatment has been completed, any remaining suspension
1252 should not be reused.

1253

1254

1255 **References:** 1. National Committee for Clinical Laboratory Standards, Methods for
1256 Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-Fifth
1257 Edition. Approved Standard NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS,
1258 Wayne, PA, January 2000.

- 1259 2. National Committee for Clinical Laboratory Standards, Performance Standards
 1260 for Antimicrobial Disk Susceptibility Tests-Seventh Edition. Approved Standard
 1261 NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.
 1262 3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug
 1263 Product's Advisory Committee meeting, March 31, 1993, Silver Spring MD. Report
 1264 available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901
 1265 Chapman Avenue, Room 200, Rockville, MD 20852, USA
 1266 4. 21 CFR 314.510 (Subpart H – Accelerated Approval of New Drugs for Life-
 1267 Threatening Illnesses)
 1268 5. Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin
 1269 during prolonged therapy in rhesus monkeys J Infect Dis 1992; 166: 1184-7.
 1270 6. Friedlander AM, et al. Postexposure prophylaxis against experimental
 1271 inhalational anthrax J Infect Dis 1993; 167: 1239-42.

1272
 1273

1274 **Rx Only**

1275 PX##### 8/00 Bay o 9867 5202-2-A-U.S.-10 © 2000 Bayer Corporation XXXX
 1276 CIPRO (R) (ciprofloxacin) 5% and 10% Oral Suspension Made in Italy. Printed in
 1277 U.S.A.

1278
 1279
 1280
 1281
 1282
 1283
 1284
 1285

1286 **CIPRO® I.V.**
 1287 **(ciprofloxacin)**
 1288 **For Intravenous Infusion**

1289
 1290

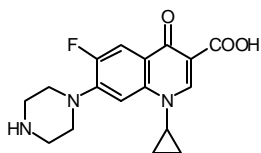
PZXXXXXX

8/29/00

1291
 1292

DESCRIPTION

1293 CIPRO® I.V. (ciprofloxacin) is a synthetic broad-spectrum antimicrobial agent for
 1294 intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-
 1295 6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical
 1296 formula is C₁₇H₁₈FN₃O₃ and its chemical structure is:
 1297



Ciprofloxacin

1298
1299

1300 Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of
1301 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in
1302 water and ethanol. Ciprofloxacin differs from other quinolones in that it has a
1303 fluorine atom at the 6-position, a piperazine moiety at the 7-position, and a
1304 cyclopropyl ring at the 1-position. CIPRO® I.V. solutions are available as sterile
1305 1.0% aqueous concentrates, which are intended for dilution prior to administration,
1306 and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulas
1307 contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment.
1308 The pH range for the 1% aqueous concentrates in vials is 3.3 to 3.9. The pH range
1309 for the 0.2% ready-for-use infusion solutions is 3.5 to 4.6.

1310

1311 The plastic container is fabricated from a specially formulated polyvinyl chloride.
1312 Solutions in contact with the plastic container can leach out certain of its chemical
1313 components in very small amounts within the expiration period, e.g., di(2-ethylhexyl)
1314 phthalate (DEHP), up to 5 parts per million. The suitability of the plastic has been
1315 confirmed in tests in animals according to USP biological tests for plastic
1316 containers as well as by tissue culture toxicity studies.

1317

1318

CLINICAL PHARMACOLOGY

1319

1320 Following 60-minute intravenous infusions of 200 mg and 400 mg ciprofloxacin to
1321 normal volunteers, the mean maximum serum concentrations achieved were 2.1
1322 and 4.6 µg/mL, respectively; the concentrations at 12 hours were 0.1 and 0.2
1323 µg/mL, respectively.

1324

1325

Steady-state Ciprofloxacin Serum Concentrations ($\mu\text{g/mL}$)

1326

After 60-minute I.V. Infusions q 12 h.

1327

1328

Time after starting the infusion

1329

1330

Dose	30 min.	1 hr	3 hr	6 hr	8 hr	12 hr
200 mg	1.7	2.1	0.6	0.3	0.2	0.1
400 mg	3.7	4.6	1.3	0.7	0.5	0.2

1331

1332

1333

1334

1335

1336

1337

1338

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. The serum elimination half-life is approximately 5-6 hours and the total clearance is around 35 L/hr. Comparison of the pharmacokinetic parameters following the 1st and 5th I.V. dose on a q 12 h regimen indicates no evidence of drug accumulation.

1339

1340

1341

1342

1343

1344

1345

1346

1347

1348

1349

1350

1351

Steady-state Pharmacokinetic Parameter

1352

Following Multiple Oral and I.V. Doses

1353

1354

1355

1356

1357

1358

1359

1360

Parameters	500 mg q12h, P.O.	400 mg 12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	13.7 ^a	12.7 ^a	31.6 ^b	32.9 ^c
C_{max} ($\mu\text{g/mL}$)	2.97	4.56	3.59	4.07

^aAUC_{0-12h} ^bAUC_{24h}=AUC_{0-12h} \times 2 ^cAUC_{24h}=AUC_{0-8h} \times 3

1361

1362

1363

1364

1365

1366

1367

After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg I.V. dose, concentrations in the urine usually exceed 200 $\mu\text{g/mL}$ 0-2 hours after dosing and are generally greater than 15 $\mu\text{g/mL}$ 8-12 hours after dosing. Following a 400- mg I.V. dose, urine concentrations generally exceed 400 $\mu\text{g/mL}$ 0-2 hours after dosing and are usually greater that 30 $\mu\text{g/mL}$ 8-12 hours after dosing. The renal clearance is

1368 approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by
1369 24 hours after dosing.

1370

1371 The serum concentrations of ciprofloxacin and metronidazole were not altered when
1372 these two drugs were given concomitantly.

1373

1374 Co-administration of probenecid with ciprofloxacin results in about a 50% reduction
1375 in the ciprofloxacin renal clearance and a 50% increase in its concentration in the
1376 systemic circulation. Although bile concentrations of ciprofloxacin are several fold
1377 higher than serum concentrations after intravenous dosing, only a small amount of
1378 the administered dose (<1%) is recovered from the bile as unchanged drug.

1379 Approximately 15% of an I.V. dose is recovered from the feces within 5 days after
1380 dosing.

1381

1382 After I.V. administration, three metabolites of ciprofloxacin have been identified in
1383 human urine which together account for approximately 10% of the intravenous dose.

1384

1385 Pharmacokinetic studies of the oral (single dose) and intravenous (single and
1386 multiple dose) forms of ciprofloxacin indicate that plasma concentrations of
1387 ciprofloxacin are higher in elderly subjects (>65 years) as compared to young
1388 adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is
1389 approximately 30%, and can be at least partially attributed to decreased renal
1390 clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the
1391 elderly. These differences are not considered clinically significant. (See

1392 **PRECAUTIONS: Geriatric Use.**)

1393

1394 In patients with reduced renal function, the half-life of ciprofloxacin is slightly
1395 prolonged and dosage adjustments may be required. (See **DOSAGE AND**
1396 **ADMINISTRATION.**)

1397

1398 In preliminary studies in patients with stable chronic liver cirrhosis, no significant
1399 changes in ciprofloxacin pharmacokinetics have been observed. However, the
1400 kinetics of ciprofloxacin in patients with acute hepatic insufficiency have not been
1401 fully elucidated.

1402

1403 Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with
1404 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin
1405 concentrations were 3.02 $\mu\text{g/mL}$ $\frac{1}{2}$ hour and 1.18 $\mu\text{g/mL}$ between 6-8 hours after
1406 the end of infusion.

1407

1408 The binding of ciprofloxacin to serum proteins is 20 to 40%.

1409

1410 After intravenous administration, ciprofloxacin is present in saliva, nasal and
1411 bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and
1412 prostatic secretions. It has also been detected in the lung, skin, fat, muscle,

1413 cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF
1414 concentrations are generally less than 10% of peak serum concentrations. Levels
1415 of the drug in the aqueous and vitreous chambers of the eye are lower than in
1416 serum.

1417

1418 **Microbiology:** Ciprofloxacin has *in vitro* activity against a wide range of gram-
1419 negative and gram-positive microorganisms. The bactericidal action of
1420 ciprofloxacin results from interference with the enzyme DNA gyrase which is needed
1421 for the synthesis of bacterial DNA.

1422

1423 Ciprofloxacin has been shown to be active against most strains of the following
1424 microorganisms, both *in vitro* and in clinical infections as described in the
1425 **INDICATIONS AND USAGE** section of the package insert for CIPRO® I.V.
1426 (ciprofloxacin for intravenous infusion).

1427

1428 **Aerobic gram-positive microorganisms**

1429 *Enterococcus faecalis* (Many strains are only moderately susceptible.)

1430 *Staphylococcus aureus* (methicillin susceptible)

1431 *Staphylococcus epidermidis*

1432 *Staphylococcus saprophyticus*

1433 *Streptococcus pneumoniae*

1434 *Streptococcus pyogenes*

1435

1436 **Aerobic gram-negative microorganisms**

1437 *Citrobacter diversus* *Morganella morganii*

1438 *Citrobacter freundii* *Proteus mirabilis*

1439 *Enterobacter cloacae* *Proteus vulgaris*

1440 *Escherichia coli* *Providencia rettgeri*

1441 *Haemophilus influenzae* *Providencia stuartii*

1442 *Haemophilus parainfluenzae* *Pseudomonas aeruginosa*

1443 *Klebsiella pneumoniae* *Serratia marcescens*

1444 *Moraxella catarrhalis*

1445

1446 Ciprofloxacin has been shown to be active against most strains of the following
1447 microorganisms, both *in vitro* and in clinical infections as described in the
1448 **INDICATIONS AND USAGE** section of the package insert for CIPRO®
1449 (ciprofloxacin hydrochloride) Tablets.

1450

1451 **Aerobic gram-positive microorganisms**

1452

1453 *Enterococcus faecalis* (Many strains are only moderately susceptible.)

1454 *Staphylococcus aureus* (methicillin susceptible)

1455 *Staphylococcus epidermidis*

1456 *Staphylococcus saprophyticus*
1457 *Streptococcus pneumoniae*
1458 *Streptococcus pyogenes*

1459

1460 **Aerobic gram-negative microorganisms**

1461	<i>Campylobacter jejuni</i>	<i>Proteus mirabilis</i>
1462	<i>Citrobacter diversus</i>	<i>Proteus vulgaris</i>
1463	<i>Citrobacter freundii</i>	<i>Providencia rettgeri</i>
1464	<i>Enterobacter cloacae</i>	<i>Providencia stuartii</i>
1465	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
1466	<i>Haemophilus influenzae</i>	<i>Salmonella typhi</i>
1467	<i>Haemophilus parainfluenzae</i>	<i>Serratia marcescens</i>
1468	<i>Klebsiella pneumoniae</i>	<i>Shigella boydii</i>
1469	<i>Moraxella catarrhalis</i>	<i>Shigella dysenteriae</i>
1470	<i>Morganella morganii</i>	<i>Shigella flexneri</i>
1471	<i>Neisseria gonorrhoeae</i>	<i>Shigella sonnei</i>

1472

1473 Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro*
1474 and by use of serum levels as a surrogate marker (see **INDICATIONS AND**
1475 **USAGE** and **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

1476

1477 The following *in vitro* data are available, but their clinical significance is
1478 unknown.

1479

1480 Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL
1481 or less against most (≥90%) strains of the following microorganisms; however, the
1482 safety and effectiveness of ciprofloxacin in treating clinical infections due to these
1483 microorganisms have not been established in adequate and well-controlled clinical
1484 trials.

1485

1486 **Aerobic gram-positive microorganisms**

1487 *Staphylococcus haemolyticus*
1488 *Staphylococcus hominis*

1489

1490 **Aerobic gram-negative microorganisms**

1491	<i>Acinetobacter lwoffii</i>	<i>Pasteurella multocida</i>
1492	<i>Aeromonas hydrophila</i>	<i>Salmonella enteritidis</i>
1493	<i>Edwardsiella tarda</i>	<i>Vibrio cholerae</i>
1494	<i>Enterobacter aerogenes</i>	<i>Vibrio parahaemolyticus</i>
1495	<i>Klebsiella oxytoca</i>	<i>Vibrio vulnificus</i>
1496	<i>Legionella pneumophila</i>	<i>Yersinia enterocolitica</i>

1497

1498 Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas*
1499 *maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including
1500 *Bacteroides fragilis* and *Clostridium difficile*.

1501
1502 Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has
1503 little effect when tested *in vitro*. The minimum bactericidal concentration (MBC)
1504 generally does not exceed the minimum inhibitory concentration (MIC) by more than
1505 a factor of two. Resistance to ciprofloxacin *in vitro* usually develops slowly (multiple-
1506 step mutation).

1507
1508 Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-
1509 lactams or aminoglycosides; therefore, organisms resistant to these drugs may be
1510 susceptible to ciprofloxacin.

1511
1512 *In vitro* studies have shown that additive activity often results when ciprofloxacin is
1513 combined with other antimicrobial agents such as beta-lactams, aminoglycosides,
1514 clindamycin, or metronidazole. Synergy has been reported particularly with the
1515 combination of ciprofloxacin and a beta-lactam; antagonism is observed only rarely.

1516

1517 **Susceptibility Tests**

1518 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial
1519 minimum inhibitory concentrations (MICs). These MICs provide estimates of the
1520 susceptibility of bacteria to antimicrobial compounds. The MICs should be
1521 determined using a standardized procedure. Standardized procedures are based
1522 on a dilution method¹ (broth or agar) or equivalent with standardized inoculum
1523 concentrations and standardized concentrations of ciprofloxacin powder. The MIC
1524 values should be interpreted according to the following criteria:

1525

1526 For testing aerobic microorganisms other than *Haemophilus influenzae*,
1527 *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*^a:

1528

1529 <u>MIC (mg/mL)</u>	1529 <u>Interpretation</u>
1530 ≤ 1	1530 Susceptible (S)
1531 2	1531 Intermediate (I)
1532 ≥ 4	1532 Resistant (R)

1533

1534 ^aThese interpretive standards are applicable only to broth microdilution
1535 susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with
1536 2-5% lysed horse blood.

1537

1538 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

1539

1540 <u>MIC (mg/mL)</u>	1540 <u>Interpretation</u>
1541 ≤ 1	1541 Susceptible (S)

1542

1543 ^b This interpretive standard is applicable only to broth microdilution susceptibility
1544 tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using
1545 *Haemophilus* Test Medium¹.

1546

1547 The current absence of data on resistant strains precludes defining any results other
1548 than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible “
1549 category should be submitted to a reference laboratory for further testing.

1550

1551 For testing *Neisseria gonorrhoeae* ^c:

1552

1553 **MIC (mg/mL)**

Interpretation

1554 ≤ 0.06

Susceptible (S)

1555

1556 ^c This interpretive standard is applicable only to agar dilution test with GC agar base
1557 and 1% defined growth supplement.

1558

1559 The current absence of data on resistant strains precludes defining any results other
1560 than “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible”
1561 category should be submitted to a reference laboratory for further testing.

1562

1563 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the
1564 antimicrobial compound in the blood reaches the concentrations usually achievable.
1565 A report of “Intermediate” indicates that the result should be considered equivocal,
1566 and, if the microorganism is not fully susceptible to alternative, clinically feasible
1567 drugs, the test should be repeated. This category implies possible clinical
1568 applicability in body sites where the drug is physiologically concentrated or in
1569 situations where high dosage of drug can be used. This category also provides a
1570 buffer zone which prevents small uncontrolled technical factors from causing major
1571 discrepancies in interpretation. A report of “Resistant” indicates that the pathogen
1572 is not likely to be inhibited if the antimicrobial compound in the blood reaches the
1573 concentrations usually achievable; other therapy should be selected.

1574

1575 Standardized susceptibility test procedures require the use of laboratory control
1576 microorganisms to control the technical aspects of the laboratory procedures.
1577 Standard ciprofloxacin powder should provide the following MIC values:

1578

1579 **Organism**

MIC (µg/mL)

1580

1581 *E. faecalis*

ATCC 29212

0.25-2.0

1582 *E. coli*

ATCC 25922

0.004-0.015

1583 *H. influenzae*^a

ATCC 49247

0.004-0.03

1584 *N. gonorrhoeae*^b

ATCC 49226

0.001-0.008

1585 *P. aeruginosa*

ATCC 27853

0.25-1.0

1586 *S. aureus* ATCC 29213 0.12-0.5

1587

1588 ^a This quality control range is applicable to only *H. influenzae* ATCC 49247 tested
1589 by a broth microdilution procedure using *Haemophilus* Test Medium (HTM)¹.

1590

1591 ^b This quality control range is applicable to only *N. gonorrhoeae* ATCC 49226
1592 tested by an agar dilution procedure using GC agar base and 1% defined growth
1593 supplement.

1594

1595 **Diffusion Techniques:** Quantitative methods that require measurement of zone
1596 diameters also provide reproducible estimates of the susceptibility of bacteria to
1597 antimicrobial compounds. One such standardized procedure² requires the use
1598 of standardized inoculum concentrations. This procedure uses paper disks
1599 impregnated with 5- μ g ciprofloxacin to test the susceptibility of microorganisms to
1600 ciprofloxacin.

1601

1602 Reports from the laboratory providing results of the standard single-disk
1603 susceptibility test with a 5- μ g ciprofloxacin disk should be interpreted according to
1604 the following criteria:

1605

1606 For testing aerobic microorganisms other than *Haemophilus influenzae*,
1607 *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*^a:

1608

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥ 21	Susceptible (S)
16-20	Intermediate (I)
≤ 15	Resistant (R)

1613

1614 ^a These zone diameter standards are applicable only to tests performed for
1615 streptococci using Mueller-Hinton agar supplemented with 5% sheep blood
1616 incubated in 5% CO₂.

1617

1618 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

1619

<u>Zone Diameter(mm)</u>	<u>Interpretation</u>
≥ 21	Susceptible (S)

1622

1623 ^b This zone diameter standard is applicable only to tests with *Haemophilus*
1624 *influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium
1625 (HTM)².

1626

1627 The current absence of data on resistant strains precludes defining any results other
1628 than "Susceptible". Strains yielding zone diameter results suggestive of a

1629 “nonsusceptible” category should be submitted to a reference laboratory for further
1630 testing.

1631 For testing *Neisseria gonorrhoeae*^c:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
≥36	Susceptible (S)

1635
1636 ^c This zone diameter standard is applicable only to disk diffusion tests with GC agar
1637 base and 1% defined growth supplement.

1638
1639 The current absence of data on resistant strains precludes defining any results other
1640 than “Susceptible”. Strains yielding zone diameter results suggestive of a
1641 “nonsusceptible” category should be submitted to a reference laboratory for further
1642 testing.

1643
1644 Interpretation should be as stated above for results using dilution techniques.
1645 Interpretation involves correlation of the diameter obtained in the disk test with the
1646 MIC for ciprofloxacin.

1647
1648 As with standardized dilution techniques, diffusion methods require the use of
1649 laboratory control microorganisms that are used to control the technical aspects of
1650 the laboratory procedures. For the diffusion technique, the 5-μg ciprofloxacin disk
1651 should provide the following zone diameters in these laboratory test quality control
1652 strains:

<u>Organism</u>		<u>Zone Diameter (mm)</u>
<i>E. coli</i>	ATCC 25922	30-40
<i>H. influenzae</i> ^a	ATCC 49247	34-42
<i>N. gonorrhoeae</i> ^b	ATCC 49226	48-58
<i>P. aeruginosa</i>	ATCC 27853	25-33
<i>S. aureus</i>	ATCC 25923	22-30

1660
1661 ^aThese quality control limits are applicable to only *H. influenzae* ATCC 49247
1662 testing using *Haemophilus* Test Medium (HTM)².

1663
1664 ^b These quality control limits are applicable only to tests conducted with *N.*
1665 *gonorrhoeae* ATCC 49226 performed by disk diffusion using GC agar base and
1666 1% defined growth supplement.

1667 INDICATIONS AND USAGE

1668
1669

1670 CIPRO® I.V. is indicated for the treatment of infections caused by susceptible
1671 strains of the designated microorganisms in the conditions listed below when the
1672 intravenous administration offers a route of administration advantageous to the
1673 patient. Please see **DOSAGE AND ADMINISTRATION** for specific
1674 recommendations.

1675
1676 **Urinary Tract Infections** caused by *Escherichia coli* (including cases with
1677 secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae*,
1678 *Enterobacter cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia*
1679 *rettgeri*, *Morganella morganii*, *Citrobacter diversus*, *Citrobacter freundii*,
1680 *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus*
1681 *saprophyticus*, or *Enterococcus faecalis*.

1682
1683 **Lower Respiratory Infections** caused by *Escherichia coli*, *Klebsiella*
1684 *pneumoniae* subspecies *pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*,
1685 *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Haemophilus*
1686 *parainfluenzae*, or *Streptococcus pneumoniae*.

1687
1688 NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in
1689 the treatment of presumed or confirmed pneumonia secondary to *Streptococcus*
1690 *pneumoniae*.

1691
1692 **Nosocomial Pneumonia** caused by *Haemophilus influenzae* or *Klebsiella*
1693 *pneumoniae*.

1694
1695 **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella*
1696 *pneumoniae* subspecies *pneumoniae*, *Enterobacter cloacae*, *Proteus mirabilis*,
1697 *Proteus vulgaris*, *Providencia stuartii*, *Morganella morganii*, *Citrobacter freundii*,
1698 *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin susceptible),
1699 *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

1700
1701 **Bone and Joint Infections** caused by *Enterobacter cloacae*, *Serratia*
1702 *marcescens*, or *Pseudomonas aeruginosa*.

1703
1704 **Complicated Intra-Abdominal Infections** (used in conjunction with
1705 metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus*
1706 *mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*. (See **DOSAGE AND**
1707 **ADMINSTRATION.**)

1708
1709 **Acute Sinusitis** caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*,
1710 or *Moraxella catarrhalis*.

1711 **Chronic Bacterial Prostatitis** caused by *Escherichia coli* or *Proteus mirabilis*.
1712

1713 **Empirical Therapy for Febrile Neutropenic Patients** in combination with
1714 piperacillin sodium. (See **DOSAGE AND ADMINISTRATION** and **CLINICAL**
1715 **STUDIES**.)
1716

1717 **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of
1718 disease following exposure to aerosolized *Bacillus anthracis*.
1719

1720 Ciprofloxacin serum concentrations achieved in humans serve as a surrogate
1721 endpoint reasonably likely to predict clinical benefit and provide the basis for this
1722 indication.⁴ (See also, **INHALATIONAL ANTHRAX – ADDITIONAL**
1723 **INFORMATION**).
1724

1725 If anaerobic organisms are suspected of contributing to the infection, appropriate
1726 therapy should be administered.
1727

1728 Appropriate culture and susceptibility tests should be performed before treatment in
1729 order to isolate and identify organisms causing infection and to determine their
1730 susceptibility to ciprofloxacin. Therapy with CIPRO® I.V. may be initiated before
1731 results of these tests are known; once results become available, appropriate
1732 therapy should be continued.
1733

1734 As with other drugs, some strains of *Pseudomonas aeruginosa* may develop
1735 resistance fairly rapidly during treatment with ciprofloxacin. Culture and
1736 susceptibility testing performed periodically during therapy will provide information
1737 not only on the therapeutic effect of the antimicrobial agent but also on the possible
1738 emergence of bacterial resistance.
1739

1740 **CLINICAL STUDIES**

1741

1742 **EMPIRICAL THERAPY IN FEBRILE NEUTROPENIC PATIENTS**

1743

1744 The safety and efficacy of ciprofloxacin, 400 mg I.V. q 8h, in combination with
1745 piperacillin sodium, 50 mg/kg I.V. q 4h, for the empirical therapy of febrile
1746 neutropenic patients were studied in one large pivotal multicenter, randomized trial
1747 and were compared to those of tobramycin, 2 mg/kg I.V. q 8h, in combination with
1748 piperacillin sodium, 50 mg/kg I.V. q 4h.
1749

1750 The demographics of the evaluable patients were as follows:
1751

1752			
1753	Total	Ciprofloxacin/Piperacillin	Tobramycin/Piperacillin

	N=233	N=237
1754		
1755		
1756	Median Age (years)	47.0 (range 19-84)
1757	Male	114 (48.9%)
1758	Female	119 (51.1%)
1759	Leukemia/Bone Marrow	165 (70.8%)
1760	Transplant	
1761	Solid Tumor/Lymphoma	68 (29.2%)
1762	Median Duration of	15.0 (range 1-61)
1763	Neutropenia (days)	14.0 (range 1-89)

1764 Clinical response rates observed in this study were as follows:

1765		Ciprofloxacin/Piperacillin	Tobramycin/Piperacillin
1766	Outcomes	N=233	N=237
1767		Success (%)	Success (%)
1768		Success (%)	Success (%)
1769			
1770	Clinical Resolution of	63 (27.0%)	52 (21.9%)
1771	Initial Febrile Episode with		
1772	No Modifications of		
1773	Empirical Regimen*		
1774			
1775	Clinical Resolution of	187 (80.3%)	185 (78.1%)
1776	Initial Febrile Episode		
1777	Including Patients with		
1778	Modifications of		
1779	Empirical Regimen		
1780			
1781	Overall Survival	224 (96.1%)	223 (94.1%)

1782

1783 *To be evaluated as a clinical resolution, patients had to have: (1) resolution of

1784 fever; (2) microbiological eradication of infection (if an infection was

1785 microbiologically documented); (3) resolution of signs/symptoms of infection; and

1786 (4) no modification of empirical antibiotic regimen.

1787 **CONTRAINDICATIONS**

1788

1789

1790 CIPRO® I.V. (ciprofloxacin) is contraindicated in persons with history of

1791 hypersensitivity to ciprofloxacin or any member of the quinolone class of

1792 antimicrobial agents.

1793 **WARNINGS**

1794

1795

1796 **THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC**
1797 **PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), , -**
1798 **EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE),**
1799 **PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN**
1800 **ESTABLISHED. (See PRECAUTIONS: Pediatric Use, Pregnancy, and**
1801 **Nursing Mothers subsections.)** Ciprofloxacin causes lameness in immature dogs.
1802 Histopathological examination of the weight-bearing joints of these dogs revealed
1803 permanent lesions of the cartilage. Related quinolone-class drugs also produce
1804 erosions of cartilage of weight-bearing joints and other signs of arthropathy in
1805 immature animals of various species. (See **ANIMAL PHARMACOLOGY.**)

1806
1807 Convulsions, increased intracranial pressure and toxic psychosis have been
1808 reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may
1809 also cause central nervous system (CNS) events including: dizziness, confusion,
1810 tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These
1811 reactions may occur following the first dose. If these reactions occur in patients
1812 receiving ciprofloxacin, the drug should be discontinued and appropriate measures
1813 instituted. As with all quinolones, ciprofloxacin should be used with caution in
1814 patients with known or suspected CNS disorders that may predispose to seizures
1815 or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in
1816 the presence of other risk factors that may predispose to seizures or lower the
1817 seizure threshold (e.g. certain drug therapy, renal dysfunction). (See
1818 **PRECAUTIONS: General, Information for Patients, Drug Interaction and**
1819 **ADVERSE REACTIONS.**)

1820
1821 **SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS**
1822 **RECEIVING CONCURRENT ADMINISTRATION OF INTRAVENOUS**
1823 **CIPROFLOXACIN AND THEOPHYLLINE.** These reactions have included
1824 cardiac arrest, seizure, status epilepticus, and respiratory failure. Although similar
1825 serious adverse events have been reported in patients receiving theophylline alone,
1826 the possibility that these reactions may be potentiated by ciprofloxacin cannot be
1827 eliminated. If concomitant use cannot be avoided, serum levels of theophylline
1828 should be monitored and dosage adjustments made as appropriate.

1829
1830 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some
1831 following the first dose, have been reported in patients receiving quinolone therapy.
1832 Some reactions were accompanied by cardiovascular collapse, loss of
1833 consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching.
1834 Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic
1835 reactions require immediate emergency treatment with epinephrine and other
1836 resuscitation measures, including oxygen, intravenous fluids, intravenous
1837 antihistamines, corticosteroids, pressor amines, and airway management, as
1838 clinically indicated.

1839 Severe hypersensitivity reactions characterized by rash, fever, eosinophilia,
1840 jaundice, and hepatic necrosis with fatal outcome have also been reported
1841 extremely rarely in patients receiving ciprofloxacin along with other drugs. The
1842 possibility that these reactions were related to ciprofloxacin cannot be excluded.
1843 Ciprofloxacin should be discontinued at the first appearance of a skin rash or any
1844 other sign of hypersensitivity.
1845

1846 **Pseudomembranous colitis has been reported with nearly all antibacterial**
1847 **agents, including ciprofloxacin, and may range in severity from mild to life-**
1848 **threatening. Therefore, it is important to consider this diagnosis in patients**
1849 **who present with diarrhea subsequent to the administration of antibacterial**
1850 **agents.**
1851

1852 Treatment with antibacterial agents alters the normal flora of the colon and may
1853 permit overgrowth of clostridia. Studies indicate that a toxin produced by
1854 *Clostridium difficile* is one primary cause of “antibiotic-associated colitis.”
1855

1856 After the diagnosis of pseudomembranous colitis has been established, therapeutic
1857 measures should be initiated. Mild cases of pseudomembranous colitis usually
1858 respond to drug discontinuation alone. In moderate to severe cases, consideration
1859 should be given to management with fluids and electrolytes, protein
1860 supplementation, and treatment with an antibacterial drug clinically effective against
1861 *C. difficile* colitis.
1862

1863 Achilles and other tendon ruptures that required surgical repair or resulted in
1864 prolonged disability have been reported with ciprofloxacin and other quinolones.
1865 Ciprofloxacin should be discontinued if the patient experiences pain, inflammation,
1866 or rupture of a tendon.
1867

1868 PRECAUTIONS

1869 **General:** INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY
1870 SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local I.V. site reactions
1871 have been reported with the intravenous administration of ciprofloxacin. These
1872 reactions are more frequent if infusion time is 30 minutes or less or if small veins of
1873 the hand are used. (See **ADVERSE REACTIONS**.)
1874

1875 Quinolones, including ciprofloxacin, may also cause central nervous system (CNS)
1876 events, including: nervousness, agitation, insomnia, anxiety, nightmares or
1877 paranoia. (See **WARNINGS, Information for Patients, and Drug Interactions**.)
1878
1879

1880

1881 Crystals of ciprofloxacin have been observed rarely in the urine of human subjects
1882 but more frequently in the urine of laboratory animals, which is usually alkaline. (See
1883 **ANIMAL PHARMACOLOGY**.) Crystalluria related to ciprofloxacin has been
1884 reported only rarely in humans because human urine is usually acidic. Alkalinity of
1885 the urine should be avoided in patients receiving ciprofloxacin. Patients should be
1886 well hydrated to prevent the formation of highly concentrated urine.

1887
1888 Alteration of the dosage regimen is necessary for patients with impairment of renal
1889 function. (See **DOSAGE AND ADMINISTRATION**.)

1890
1891 Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction
1892 has been observed in some patients who were exposed to direct sunlight while
1893 receiving some members of the quinolone class of drugs. Excessive sunlight
1894 should be avoided.

1895
1896 As with any potent drug, periodic assessment of organ system functions, including
1897 renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

1898
1899 **Information For Patients:** Patients should be advised that ciprofloxacin may be
1900 associated with hypersensitivity reactions, even following a single dose, and to
1901 discontinue the drug at the first sign of a skin rash or other allergic reaction.

1902
1903 Ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should
1904 know how they react to this drug before they operate an automobile or machinery or
1905 engage in activities requiring mental alertness or coordination.

1906
1907 Patients should be advised that ciprofloxacin may increase the effects of
1908 theophylline and caffeine. There is a possibility of caffeine accumulation when
1909 products containing caffeine are consumed while taking ciprofloxacin.

1910
1911 Patients should be advised to discontinue treatment; rest and refrain from exercise;
1912 and inform their physician if they experience pain, inflammation, or rupture of a
1913 tendon.

1914
1915 Patients should be advised that convulsions have been reported in patients taking
1916 quinolones, including ciprofloxacin, and to notify their physician before taking this
1917 drug if there is a history of this condition.

1918
1919 **Drug Interactions:** As with some other quinolones, concurrent administration of
1920 ciprofloxacin with theophylline may lead to elevated serum concentrations of
1921 theophylline and prolongation of its elimination half-life. This may result in increased
1922 risk of theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant

1923 use cannot be avoided, serum levels of theophylline should be monitored and
1924 dosage adjustments made as appropriate.

1925
1926 Some quinolones, including ciprofloxacin, have also been shown to interfere with the
1927 metabolism of caffeine. This may lead to reduced clearance of caffeine and
1928 prolongation of its serum half-life.

1929
1930 Some quinolones, including ciprofloxacin, have been associated with transient
1931 elevations in serum creatinine in patients receiving cyclosporine concomitantly.

1932
1933 Altered serum levels of phenytoin (increased and decreased) have been reported in
1934 patients receiving concomitant ciprofloxacin.

1935
1936 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has,
1937 in some patients, resulted in severe hypoglycemia. Fatalities have been reported.

1938
1939 Quinolones have been reported to enhance the effects of the oral anticoagulant
1940 warfarin or its derivatives. When these products are administered concomitantly,
1941 prothrombin time or other suitable coagulation tests should be closely monitored.

1942
1943 Probenecid interferes with renal tubular secretion of ciprofloxacin and produces an
1944 increase in the level of ciprofloxacin in the serum. This should be considered if
1945 patients are receiving both drugs concomitantly.

1946
1947 As with other broad-spectrum antimicrobial agents, prolonged use of ciprofloxacin
1948 may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the
1949 patient's condition and microbial susceptibility testing are essential. If
1950 superinfection occurs during therapy, appropriate measures should be taken.

1951
1952 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Eight *in vitro*
1953 mutagenicity tests have been conducted with ciprofloxacin. Test results are listed
1954 below:

1955
1956 Salmonella/Microsome Test (Negative)
1957 *E. coli* DNA Repair Assay (Negative)
1958 Mouse Lymphoma Cell Forward Mutation Assay (Positive)
1959 Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
1960 Syrian Hamster Embryo Cell Transformation Assay (Negative)
1961 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
1962 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay
1963 (Negative)
1964 Rat Hepatocyte DNA Repair Assay (Positive)
1965

1966 Thus, two of the eight tests were positive, but results of the following three *in vivo*
1967 test systems gave negative results:

1968

1969 Rat Hepatocyte DNA Repair Assay

1970 Micronucleus Test (Mice)

1971 Dominant Lethal Test (Mice)

1972

1973 Long-term carcinogenicity studies in mice and rats have been completed. After
1974 daily oral doses of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up
1975 to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or
1976 tumorigenic effects in these species.

1977

1978 Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not
1979 reduce the time to appearance of UV-induced skin tumors as compared to vehicle
1980 control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times
1981 every two weeks for up to 78 weeks while concurrently being administered
1982 ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice
1983 treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal
1984 to maximum recommended human dose based upon mg/m²), as opposed to 34
1985 weeks when animals were treated with both UVA and vehicle. The times to
1986 development of skin tumors ranged from 16-32 weeks in mice treated concomitantly
1987 with UVA and other quinolones.³

1988

1989 In this model, mice treated with ciprofloxacin alone did not develop skin or systemic
1990 tumors. There are no data from similar models using pigmented mice and/or fully
1991 haired mice. The clinical significance of these findings to humans is unknown.

1992

1993 Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8
1994 times the highest recommended human dose of 1200 mg based upon body surface
1995 area) revealed no evidence of impairment.

1996

1997 **Pregnancy: Teratogenic Effects. Pregnancy Category C:** Reproduction
1998 studies have been performed in rats and mice using oral doses of up to 100mg/kg
1999 (0.8 and 0.4 times the maximum daily human dose based upon body surface area,
2000 respectively) and I.V. doses of up to 30 mg/kg (0.24 and 0.12 times the maximum
2001 daily human dose based upon body surface area, respectively) and have revealed
2002 no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30
2003 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal
2004 weight loss and an increased incidence of abortion, but no teratogenicity was
2005 observed at either dose. After intravenous administration of doses up to 20 mg/kg,
2006 no maternal toxicity was produced in the rabbit, and no embryotoxicity or
2007 teratogenicity was observed. There are, however, no adequate and well-controlled
2008 studies in pregnant women. Ciprofloxacin should be used during pregnancy only if
2009 the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

2010

2011 **Nursing Mothers:** Ciprofloxacin is excreted in human milk. Because of the
2012 potential for serious adverse reactions in infants nursing from mothers taking
2013 ciprofloxacin, a decision should be made whether to discontinue nursing or to
2014 discontinue the drug, taking into account the importance of the drug to the mother.

2015
2016 **Pediatric Use:** Safety and effectiveness in pediatric patients and adolescents less
2017 than 18 years of age have not been established, except for use in inhalational
2018 anthrax (post-exposure). Ciprofloxacin causes arthropathy in juvenile animals. (See
2019 **WARNINGS**.)

2020
2021 For the indication of inhalational anthrax (post-exposure), the risk-benefit
2022 assessment indicates that administration of ciprofloxacin to pediatric patients is
2023 appropriate. For information regarding pediatric dosing in inhalational anthrax
2024 (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL**
2025 **ANTHRAX – ADDITIONAL INFORMATION**.

2026
2027 Short-term safety data from a single trial in pediatric cystic fibrosis patients are
2028 available. In a randomized, double-blind clinical trial for the treatment of acute
2029 pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients
2030 received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by
2031 ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62
2032 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and
2033 tobramycin I.V. 3 mg/kg/dose q8h for a total of 10 - 21 days. Patients less than 5
2034 years of age were not studied. Safety monitoring in the study included periodic
2035 range of motion examinations and gait assessments by treatment-blinded
2036 examiners. Patients were followed for an average of 23 days after completing
2037 treatment (range 0-93 days). This study was not designed to determine long term
2038 effects and the safety of repeated exposure to ciprofloxacin.

2039
2040 In the study, injection site reactions were more common in the ciprofloxacin group
2041 (24%) than in the comparison group (8%). Other adverse events were similar in
2042 nature and frequency between treatment arms. Musculoskeletal adverse events
2043 were reported in 22% of the patients in the ciprofloxacin group and 21% in the
2044 comparison group. Decreased range of motion was reported in 12% of the
2045 subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia
2046 was reported in 10% of the patients in the ciprofloxacin group and 11% in the
2047 comparison group. One of sixty-seven patients developed arthritis of the knee nine
2048 days after a ten day course of treatment with ciprofloxacin. Clinical symptoms
2049 resolved, but an MRI showed knee effusion without other abnormalities eight months
2050 after treatment. However, the relationship of this event to the patient's course of
2051 ciprofloxacin can not be definitively determined, particularly since patients with
2052 cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease
2053 process.

2054

2055 **Geriatric Use:** In a retrospective analysis of 23 multiple-dose controlled clinical
2056 trials of ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25%
2057 of patients were greater than or equal to 65 years of age and 10% were greater
2058 than or equal to 75 years of age. No overall differences in safety or effectiveness
2059 were observed between these subjects and younger subjects, and other reported
2060 clinical experience has not identified differences in responses between the elderly
2061 and younger patients, but greater sensitivity of some older individuals on any drug
2062 therapy cannot be ruled out. Ciprofloxacin is known to be substantially excreted by
2063 the kidney, and the risk of adverse reactions may be greater in patients with
2064 impaired renal function. No alteration of dosage is necessary for patients greater
2065 than 65 years of age with normal renal function. However, since some older
2066 individuals experience reduced renal function by virtue of their advanced age, care
2067 should be taken in dose selection for elderly patients, and renal function monitoring
2068 may be useful in these patients. (See **CLINICAL PHARMACOLOGY** and
2069 **DOSAGE AND ADMINISTRATION**.)

2070 **ADVERSE REACTIONS**

2071
2072
2073 The most frequently reported events, without regard to drug relationship, among
2074 patients treated with intravenous ciprofloxacin were nausea, diarrhea, central
2075 nervous system disturbance, local I.V. site reactions, abnormalities of liver
2076 associated enzymes (hepatic enzymes), and eosinophilia. Headache,
2077 restlessness, and rash were also noted in greater than 1% of patients treated with
2078 the most common doses of ciprofloxacin.

2079
2080 Local I.V. site reactions have been reported with the intravenous administration of
2081 ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes
2082 or less. These may appear as local skin reactions which resolve rapidly upon
2083 completion of the infusion. Subsequent intravenous administration is not
2084 contraindicated unless the reactions recur or worsen.

2085
2086 Additional events, without regard to drug relationship or route of administration, that
2087 occurred in 1% or less of ciprofloxacin patients are listed below:

2088
2089 **CARDIOVASCULAR:** cardiovascular collapse, cardiopulmonary arrest,
2090 myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral
2091 thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina
2092 pectoris

2093 **CENTRAL NERVOUS SYSTEM:** convulsive seizures, paranoia, toxic
2094 psychosis, depression, dysphasia, phobia, depersonalization, manic
2095 reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness,
2096 lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares,
2097 weakness, drowsiness, irritability, malaise, lethargy

2098 **GASTROINTESTINAL:** ileus, jaundice, gastrointestinal bleeding, *C. difficile*
2099 associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic

2100 necrosis, intestinal perforation, dyspepsia, epigastric or abdominal pain,
2101 vomiting, constipation, oral ulceration, oral candidiasis, mouth dryness,
2102 anorexia, dysphagia, flatulence
2103 I.V. INFUSION SITE: thrombophlebitis, burning, pain, pruritus, paresthesia,
2104 erythema, swelling
2105 MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck
2106 and chest pain, achiness, flare up of gout
2107 RENAL/UROGENITAL: renal failure, interstitial nephritis, hemorrhagic
2108 cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria,
2109 urinary retention, gynecomastia, candiduria, vaginitis. Crystalluria,
2110 cylindruria, hematuria and albuminuria have also been reported.
2111 RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea,
2112 pulmonary edema, respiratory distress, pleural effusion, hemoptysis,
2113 epistaxis, hiccough
2114 SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema
2115 multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic
2116 epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck,
2117 conjunctivae, hands or lower extremities, purpura, fever, chills, flushing,
2118 pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration,
2119 hyperpigmentation, erythema nodosum, photosensitivity
2120 (See **WARNINGS**.)

2121 SPECIAL SENSES: decreased visual acuity, blurred vision, disturbed vision
2122 (flashing lights, change in color perception, overbrightness of lights,
2123 diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmus, a bad taste

2124
2125 Also reported were agranulocytosis, prolongation of prothrombin time, and
2126 possible exacerbation of myasthenia gravis.

2127
2128 Many of these events were described as only mild or moderate in severity,
2129 abated soon after the drug was discontinued, and required no treatment.

2130
2131 In several instances, nausea, vomiting, tremor, irritability, or palpitation were
2132 judged by investigators to be related to elevated serum levels of theophylline
2133 possibly as a result of drug interaction with ciprofloxacin.

2134
2135 In randomized, double-blind controlled clinical trials comparing ciprofloxacin
2136 (I.V. and I.V. P.O. sequential) with intravenous beta-lactam control antibiotics,
2137 the CNS adverse event profile of ciprofloxacin was comparable to that of the
2138 control drugs.

2139
2140 **Post-Marketing Adverse Events:** Additional adverse events, regardless of
2141 relationship to drug, reported from worldwide marketing experience with
2142 quinolones, including ciprofloxacin, are:

2143
2144 BODY AS A WHOLE: change in serum phenytoin

2145 CARDIOVASCULAR: postural hypotension, vasculitis
2146 CENTRAL NERVOUS SYSTEM: agitation, delirium,
2147 myoclonus, toxic psychosis
2148 HEMIC/LYMPHATIC: hemolytic anemia, methemoglobinemia
2149 METABOLIC/NUTRITIONAL: elevation of serum triglycerides,
2150 cholesterol, blood glucose, serum potassium
2151 MUSCULOSKELETAL: myalgia, tendinitis/tendon rupture
2152 RENAL/UROGENITAL: vaginal candidiasis
2153 (See **PRECAUTIONS.**)

2154
2155 **Adverse Laboratory Changes:** The most frequently reported changes in
2156 laboratory parameters with intravenous ciprofloxacin therapy, without regard to drug
2157 relationship are listed below:

2158
2159 Hepatic - elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase,
2160 LDH, and serum bilirubin;
2161 Hematologic - elevated eosinophil and platelet counts, decreased platelet
2162 counts, hemoglobin and/or hematocrit;
2163 Renal - elevations of serum creatinine, BUN, and uric acid;
2164 Other - elevations of serum creatinine phosphokinase, serum theophylline
2165 (in patients receiving theophylline concomitantly), blood glucose,
2166 and triglycerides.

2167
2168 Other changes occurring infrequently were: decreased leukocyte count, elevated
2169 atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of
2170 serum gamma-glutamyl transpeptidase (gamma GT), decreased BUN, decreased
2171 uric acid, decreased total serum protein, decreased serum albumin, decreased
2172 serum potassium, elevated serum potassium, elevated serum cholesterol.

2173
2174 Other changes occurring rarely during administration of ciprofloxacin were: elevation
2175 of serum amylase, decrease of blood glucose, pancytopenia, leukocytosis, elevated
2176 sedimentation rate, change in serum phenytoin, decreased prothrombin time,
2177 hemolytic anemia, and bleeding diathesis.

2178 **OVERDOSAGE**

2179
2180
2181 In the event of acute overdosage, the patient should be carefully observed and given
2182 supportive treatment. Adequate hydration must be maintained. Only a small
2183 amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or
2184 peritoneal dialysis.

2185
2186 In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions
2187 was observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

2188 **DOSAGE AND ADMINISTRATION**

2189

2190

2191 The recommended adult dosage for urinary tract infections of mild to moderate
2192 severity is 200 mg I.V. every 12 hours. For severe or complicated urinary tract
2193 infections, the recommended dosage is 400 mg I.V. every 12 hours.

2194

2195 The recommended adult dosage for lower respiratory tract infections, skin and skin
2196 structure infections, and bone and joint infections of mild to moderate severity is 400
2197 mg I.V. every 12 hours.

2198

2199 For severe/complicated infections of the lower respiratory tract, skin and skin
2200 structure, and bone and joint, the recommended adult dosage is 400 mg I.V. every 8
2201 hours.

2202

2203 The recommended adult dosage for mild, moderate, and severe nosocomial
2204 pneumonia is 400 mg I.V. every 8 hours.

2205

2206 **Complicated Intra-Abdominal Infections:** Sequential therapy [parenteral to oral -
2207 400 mg CIPRO® I.V. q12h (plus I.V. metronidazole) → 500 mg CIPRO® Tablets
2208 q12h (plus oral metronidazole)] can be instituted at the discretion of the physician.
2209 Metronidazole should be given according to product labeling to provide appropriate
2210 anaerobic coverage.

2211

2212 The recommended dosage for mild to moderate Acute Sinusitis and Chronic
2213 Bacterial Prostatitis is 400 mg I.V. every 12 hours.

2214

2215 The recommended adult dosage for empirical therapy of febrile neutropenic
2216 patients is 400 mg I.V. every 8 hours in combination with piperacillin sodium 50
2217 mg/kg I.V. q 4 hours, not to exceed 24 g/day (300 mg/kg/day), for 7-14 days.

2218

2219 The determination of dosage for any particular patient must take into consideration
2220 the severity and nature of the infection, the susceptibility of the causative
2221 microorganism, the integrity of the patient's host-defense mechanisms, and the
2222 status of renal and hepatic function.

2223

DOSAGE GUIDELINES

Intravenous

Infection †	Type or Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	200 mg	q12h	400 mg
	Severe/Complicated	400 mg	q12h	800 mg
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	1200 mg
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg
Bone and Joint	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg

Intra-Abdominal*	Complicated	400 mg	q12h	800 mg
Acute Sinusitis	Mild/Moderate	400 mg	q12h	800 mg
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	800 mg
Empirical Therapy in Febrile Neutropenic Patients	Severe			
	Ciprofloxacin + Piperacillin	400 mg 50 mg/kg	q8h q4h	1200 mg Not to exceed 24 g/day
Inhalational anthrax (post-exposure)**	Adult	400 mg	q12h	800 mg
	Pediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q12h	Not to exceed 800 mg

* used in conjunction with metronidazole. (See product labeling for prescribing information.)

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

** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans. For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

2224

2225

CIPRO® I.V. should be administered by intravenous infusion over a period of 60 minutes.

2226

2227

2228

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

2229

2230

2231

Ciprofloxacin hydrochloride (CIPRO® Tablets) for oral administration are available. Parenteral therapy may be changed to oral CIPRO® Tablets when the condition warrants, at the discretion of the physician. For complete dosage and administration information, see CIPRO® Tablets package insert.

2232

2233

2234

2235

2236

Impaired Renal Function: The following table provides dosage guidelines for use in patients with renal impairment; however, monitoring of serum drug levels provides the most reliable basis for dosage adjustment.

2237

2238

2239

2240

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

2241

2242

2243

Creatinine Clearance (mL/min)

Dosage

2244

>30

See usual dosage.

2245

5-29

200-400 mg q 18-24 hr

2246

2247

When only the serum creatinine concentration is known, the following formula may be used to estimate creatinine clearance:

2248

2249

2250

Men: Creatinine clearance (mL/min) = $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$

2251 72 x serum creatinine (mg/dL)
2252 Women: 0.85 x the value calculated for men.

2253
2254 The serum creatinine should represent a steady state of renal function.

2255
2256 For patients with changing renal function or for patients with renal impairment and
2257 hepatic insufficiency, measurement of serum concentrations of ciprofloxacin will
2258 provide additional guidance for adjusting dosage.

2259

2260

INTRAVENOUS ADMINISTRATION

2261

2262 CIPRO® I.V. should be administered by intravenous infusion over a period of 60
2263 minutes. Slow infusion of a dilute solution into a larger vein will minimize patient
2264 discomfort and reduce the risk of venous irritation.

2265

2266 **Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED**
2267 **BEFORE USE.** The intravenous dose should be prepared by aseptically
2268 withdrawing the concentrate from the vial of CIPRO® I.V. This should be diluted with
2269 a suitable intravenous solution to a final concentration of 1-2mg/mL. (See
2270 **COMPATIBILITY AND STABILITY.**) The resulting solution should be infused over
2271 a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set
2272 which may already be in place.

2273

2274 If this method or the “piggyback” method of administration is used, it is advisable to
2275 discontinue temporarily the administration of any other solutions during the infusion
2276 of CIPRO® I.V.

2277

2278 **Flexible Containers:** CIPRO® I.V. is also available as a 0.2% premixed solution in
2279 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible
2280 containers may be infused as described above.

2281

2282

COMPATIBILITY AND STABILITY

2283

2284 Ciprofloxacin injection 1% (10 mg/mL), when diluted with the following intravenous
2285 solutions to concentrations of 0.5 to 2.0 mg/mL, is stable for up to 14 days at
2286 refrigerated or room temperature storage.

2287

0.9% Sodium Chloride Injection, USP

2288

5% Dextrose Injection, USP

2289

Sterile Water for Injection

2290

10% Dextrose for Injection

2291

5% Dextrose and 0.225% Sodium Chloride for Injection

2292

5% Dextrose and 0.45% Sodium Chloride for Injection

2293

Lactated Ringer's for Injection

2294

2295 If CIPRO® I.V. is to be given concomitantly with another drug, each drug should be
2296 given separately in accordance with the recommended dosage and route of
2297 administration for each drug.
2298

2299
2300

HOW SUPPLIED

2301

2302 CIPRO® I.V. (ciprofloxacin) is available as a clear, colorless to slightly yellowish
2303 solution. CIPRO® I.V. is available in 200 mg and 400 mg strengths. The
2304 concentrate is supplied in vials while the premixed solution is supplied in flexible
2305 containers as follows:

2306

VIAL:	SIZE	STRENGTH	NDC NUMBER
	20 mL	200 mg, 1%	0026-8562-20
	40 mL	400 mg, 1%	0026-8564-64

2310

2311 **FLEXIBLE CONTAINER:** manufactured for Bayer Corporation by Abbott
2312 Laboratories, North Chicago, IL 60064.

2313

	SIZE	STRENGTH	NDC NUMBER
	100 mL 5% Dextrose	200 mg, 0.2%	0026-8552-36
	200 mL 5% Dextrose	400 mg, 0.2%	0026-8554-63

2316

2317 **FLEXIBLE CONTAINER:** manufactured for Bayer Corporation by Baxter
2318 Healthcare Corporation, Deerfield, IL 60015.

2319

	SIZE	STRENGTH	NDC NUMBER
	100 mL 5% Dextrose	200 mg, 0.2%	0026-8527-36
	200 mL 5% Dextrose	400 mg, 0.2%	0026-8527-63

2322

2323

STORAGE

2324 Vial: Store between 5-30°C (41-86°F).

2325 Flexible Container: Store between 5-25°C (41-77°F).

2326

2327 Protect from light, avoid excessive heat, protect from freezing.

2328

2329 CIPRO® I.V. (ciprofloxacin) is also available in a 120 mL Pharmacy Bulk Package.

2330

2331 Ciprofloxacin is also available as CIPRO® (ciprofloxacin HCl) Tablets 100, 250,
2332 500, and 750 mg and CIPRO® (ciprofloxacin) 5% and 10% Oral Suspension.

2333

2334

ANIMAL PHARMACOLOGY

2335

2336 Ciprofloxacin and other quinolones have been shown to cause arthropathy in
2337 immature animals of most species tested. (See **WARNINGS**.) Damage of weight-
2338 bearing joints was observed in juvenile dogs and rats. In young beagles, 100 mg/kg

2339 ciprofloxacin given daily for 4 weeks caused degenerative articular changes of the
2340 knee joint. At 30 mg/kg, the effect on the joint was minimal. In a subsequent study
2341 in beagles, removal of weight-bearing from the joint reduced the lesions but did not
2342 totally prevent them.

2343

2344 Crystalluria, sometimes associated with secondary nephropathy, occurs in
2345 laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced
2346 solubility of ciprofloxacin under alkaline conditions, which predominate in the urine
2347 of test animals; in man, crystalluria is rare since human urine is typically acidic. In
2348 rhesus monkeys, crystalluria without nephropathy has been noted after intravenous
2349 doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no
2350 nephropathological changes were noted; however, nephropathy was observed after
2351 dosing at 20 mg/kg/day for the same duration.

2352

2353 In dogs, ciprofloxacin administered at 3 and 10 mg/kg by rapid intravenous injection
2354 (15 sec.) produces pronounced hypotensive effects. These effects are considered
2355 to be related to histamine release because they are partially antagonized by
2356 pyrilamine, an antihistamine. In rhesus monkeys, rapid intravenous injection also
2357 produces hypotension, but the effect in this species is inconsistent and less
2358 pronounced.

2359

2360 In mice, concomitant administration of nonsteroidal anti-inflammatory drugs, such as
2361 phenylbutazone and indomethacin, with quinolones has been reported to enhance
2362 the CNS stimulatory effect of quinolones.

2363

2364 Ocular toxicity, seen with some related drugs, has not been observed in
2365 ciprofloxacin-treated animals.

2366

2367

2368

2368 **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**

2369

2370 The mean serum concentrations of ciprofloxacin associated with a statistically
2371 significant improvement in survival in the rhesus monkey model of inhalational
2372 anthrax are reached or exceeded in adult and pediatric patients receiving oral and
2373 intravenous regimens. (See **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin
2374 pharmacokinetics have been evaluated in various human populations. The mean
2375 peak serum concentration achieved at steady state in human adults receiving 500
2376 mg orally every 12 hours is 2.97 µg/ml, and 4.56 µg/ml following 400 mg
2377 intravenously every 12 hours. The mean trough serum concentration at steady state
2378 for both of these regimens is 0.2 µg/ml. In a study of 10 pediatric patients between 6
2379 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL
2380 and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute
2381 intravenous infusions of 10 mg/kg administered 12 hours apart. After the second
2382 intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a
2383 mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety

2384 data, including effects on cartilage, following the administration of ciprofloxacin to
2385 pediatric patients are limited. (For additional information, see **PRECAUTIONS,**
2386 **Pediatric Use.**) Ciprofloxacin serum concentrations achieved in humans serve as a
2387 surrogate endpoint reasonably likely to predict clinical benefit and provide the basis
2388 for this indication.⁴
2389

2390 A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean
2391 dose of 11 LD₅₀ (~5.5 x 10⁵) spores (range 5-30 LD₅₀) of *B. anthracis* was
2392 conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the
2393 anthrax strain used in this study was 0.08 µg/ml. In the animals studied, mean serum
2394 concentrations of ciprofloxacin achieved at expected T_{max}
2395 (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69
2396 µg/ml. Mean steady state trough concentrations at 12 hours post-dose ranged from
2397 0.12 to 0.19 µg/ml⁵. Mortality due to anthrax for animals that received a 30-day
2398 regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly
2399 lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one
2400 ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug
2401 administration period.⁶
2402

2403 **References:**

- 2404 1. National Committee for Clinical Laboratory Standards, Methods for Dilution
2405 Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fifth Edition.
2406 Approved Standard NCCLS Document M7- A5, Vol. 20, No. 2, NCCLS, Wayne,
2407 PA, January, 2000.
- 2408 2. National Committee for Clinical Laboratory Standards, Performance Standards
2409 for Antimicrobial Disk Susceptibility Tests - Seventh Edition. Approved Standard
2410 NCCLS Document M2-A7, Vol. 20, No. 1, NCCLS, Wayne, PA, January, 2000.
- 2411 3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug
2412 Products Advisory Committee Meeting, March 31, 1993, Silver Spring MD. Report
2413 available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901
2414 Chapman Avenue, Room 200, Rockville, MD 20852, USA
- 2415 4. 21 CFR 314.510 (Subpart H – Accelerated Approval of New Drugs for Life-
2416 Threatening Illnesses)
- 2417 5. Kelly DJ, et al. Serum concentrations of penicillin, doxycycline, and ciprofloxacin
2418 during prolonged therapy in rhesus monkeys J Infect Dis 1992; 166: 1184-7.
- 2419 6. Friedlander AM, et al. Postexposure prophylaxis against experimental
2420 inhalational anthrax J Infect Dis 1993; 167: 1239-42.
2421

2422
2423
2424
2425
2426
2427

Bayer Corporation
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516 USA

2428

2429 **BAYER**
2430 **Rx Only**

2431

2432 PZXXXXXX 8/00 BAY q 3939 5202-4-A-U.S.-7 ©2000 Bayer Corporation

2433 XXXX

2434 Printed in U.S.A.