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**CIPRO<sup>®</sup>**  
**(ciprofloxacin hydrochloride)**  
**TABLETS**

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**CIPRO<sup>®</sup>**  
**(ciprofloxacin\*)**  
**ORAL SUSPENSION**

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3/25/04

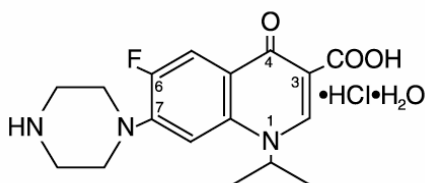
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To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO Tablets and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral Suspension should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

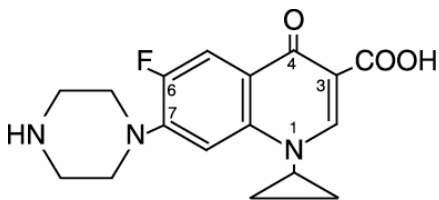
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**DESCRIPTION**

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



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



CIPRO film-coated tablets are available in 100 mg, 250 mg, 500 mg and 750 mg (ciprofloxacin equivalent) strengths. Ciprofloxacin tablets are white to slightly yellowish. The inactive ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hypromellose, titanium dioxide, polyethylene glycol and water.

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

44 Microcapsules - ciprofloxacin, povidone, methacrylic acid copolymer, hypromellose, magnesium  
45 stearate, and Polysorbate 20.

46 Diluent - medium-chain triglycerides, sucrose, lecithin, water, and strawberry flavor.

47 \* Does not comply with USP with regards to “loss on drying” and “residue on ignition”.

### 48 **CLINICAL PHARMACOLOGY**

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

53

54		<b>Maximum</b>	<b>Area</b>
55	<b>Dose</b>	<b>Serum Concentration</b>	<b>Under Curve (AUC)</b>
56	<b>(mg)</b>	<b>(µg/mL)</b>	<b>(µg•hr/mL)</b>
57	250	1.2	4.8
58	500	2.4	11.6
59	750	4.3	20.2
60	1000	5.4	30.8

61 Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12  
62 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 µg/mL, respectively. The serum  
63 elimination half-life in subjects with normal renal function is approximately 4 hours. Serum  
64 concentrations increase proportionately with doses up to 1000 mg.

65 A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum  
66 concentration time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg  
67 ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has  
68 been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion  
69 of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a C<sub>max</sub> similar to that  
70 observed with a 400 mg I.V. dose. A 250 mg oral dose given every 12 hours produces an AUC  
71 equivalent to that produced by an infusion of 200 mg ciprofloxacin given every 12 hours.

72

73	<b>Steady-state Pharmacokinetic Parameters</b>				
74	<b>Following Multiple Oral and I.V. Doses</b>				
75	Parameters	500 mg	400 mg	750 mg	400
76	mg				
77		q12h, P.O.	q12h, I.V.	q12h, P.O.	q8h,
78	I.V.				
79	AUC (µg•hr/mL)	13.7 <sup>a</sup>	12.7 <sup>a</sup>	31.6 <sup>b</sup>	32.9 <sup>c</sup>
80	C <sub>max</sub> (µg/mL)	2.97	4.56	3.59	4.07
81	<sup>a</sup> AUC <sub>0-12h</sub>				
82	<sup>b</sup> AUC <sub>24h</sub> =AUC <sub>0-12h</sub> x 2				
83	<sup>c</sup> AUC <sub>24h</sub> =AUC <sub>0-8h</sub> x 3				

84 **Distribution:** The binding of ciprofloxacin to serum proteins is 20 to 40% which is not likely to be  
85 high enough to cause significant protein binding interactions with other drugs.

86 After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue  
87 concentrations often exceed serum concentrations in both men and women, particularly in genital tissue  
88 including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial  
89 secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic  
90 secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug

91 diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10%  
92 of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous  
93 humors of the eye.

94 **Metabolism:** Four metabolites have been identified in human urine which together account for  
95 approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active  
96 than unchanged ciprofloxacin.

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

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

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

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

124 Concomitant administration of ciprofloxacin with theophylline decreases the clearance of theophylline  
125 resulting in elevated serum theophylline levels and increased risk of a patient developing CNS or  
126 other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits the formation of  
127 paraxanthine after caffeine administration. (See **PRECAUTIONS.**)

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

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

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

139 Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from  
140 4 months to 7 years, the mean C<sub>max</sub> was 2.4 mg/L (range: 1.5 – 3.4 mg/L) and the mean AUC was  
141 9.2 mg\*h/L (range: 5.8 – 14.9 mg\*h/L). There was no apparent age-dependence, and no notable  
142 increase in C<sub>max</sub> or AUC upon multiple dosing (10 mg/kg TID). In children with severe sepsis who  
143 were given intravenous ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C<sub>max</sub> was 6.1 mg/L  
144 (range: 4.6 – 8.3 mg/L) in 10 children less than 1 year of age; and 7.2 mg/L (range: 4.7 – 11.8 mg/L)  
145 in 10 children between 1 and 5 years of age. The AUC values were 17.4 mg\*h/L (range: 11.8 – 32.0  
146 mg\*h/L) and 16.5 mg\*h/L (range: 11.0 – 23.8 mg\*h/L) in the respective age groups. These values are  
147 within the range reported for adults at therapeutic doses. Based on population pharmacokinetic  
148 analysis of pediatric patients with various infections, the predicted mean half-life in children is  
149 approximately 4 - 5 hours, and the bioavailability of the oral suspension is approximately 60%.

150 **Microbiology:** Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-  
151 positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the  
152 enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA  
153 replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones,  
154 including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides,  
155 macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be  
156 susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between  
157 ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly  
158 by multiple step mutations.

159 Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when  
160 tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal  
161 inhibitory concentration (MIC) by more than a factor of 2.

162 Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both  
163 *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the  
164 package insert for CIPRO (ciprofloxacin hydrochloride) Tablets and CIPRO (ciprofloxacin\*) 5% and  
165 10% Oral Suspension.

166 **Aerobic gram-positive microorganisms**

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

168 *Staphylococcus aureus* (methicillin-susceptible strains only)

169 *Staphylococcus epidermidis* (methicillin-susceptible strains only)

170 *Staphylococcus saprophyticus*

171 *Streptococcus pneumoniae* (penicillin-susceptible strains only)

172 *Streptococcus pyogenes*

173 **Aerobic gram-negative microorganisms**

174 *Campylobacter jejuni*

*Proteus mirabilis*

175 *Citrobacter diversus*

*Proteus vulgaris*

176 *Citrobacter freundii*

*Providencia rettgeri*

177 *Enterobacter cloacae*

*Providencia stuartii*

178 *Escherichia coli*

*Pseudomonas aeruginosa*

179 *Haemophilus influenzae*

*Salmonella typhi*

180 *Haemophilus parainfluenzae*

*Serratia marcescens*

181 *Klebsiella pneumoniae*

*Shigella boydii*

182 *Moraxella catarrhalis*

*Shigella dysenteriae*

183 *Morganella morganii*

*Shigella flexneri*

184 *Neisseria gonorrhoeae* *Shigella sonnei*  
 185 Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of  
 186 serum levels as a surrogate marker (see **INDICATIONS AND USAGE** and **INHALATIONAL**  
 187 **ANTHRAX – ADDITIONAL INFORMATION**).

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

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

193 **Aerobic gram-positive microorganisms**

194 *Staphylococcus haemolyticus*

195 *Staphylococcus hominis*

196 *Streptococcus pneumoniae* (penicillin-resistant strains only)

197 **Aerobic gram-negative microorganisms**

198 *Acinetobacter Iwoffii*

*Pasteurella multocida*

199 *Aeromonas hydrophila*

*Salmonella enteritidis*

200 *Edwardsiella tarda*

*Vibrio cholerae*

201 *Enterobacter aerogenes*

*Vibrio parahaemolyticus*

202 *Klebsiella oxytoca*

*Vibrio vulnificus*

203 *Legionella pneumophila*

*Yersinia enterocolitica*

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

207 **Susceptibility Tests**

208 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory  
 209 concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial  
 210 compounds. The MICs should be determined using a standardized procedure. Standardized procedures  
 211 are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum  
 212 concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be  
 213 interpreted according to the following criteria:

214 For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*,  
 215 and *Neisseria gonorrhoeae*<sup>a</sup>:

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

220 <sup>a</sup>These interpretive standards are applicable only to broth microdilution susceptibility tests with  
 221 streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

222 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>b</sup>:

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

225 <sup>b</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with  
 226 *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium<sup>1</sup>.

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

230 For testing *Neisseria gonorrhoeae*<sup>c</sup>:

	<u>MIC (µg/mL)</u>	<u>Interpretation</u>
231	≤ 0.06	Susceptible (S)
232	0.12 – 0.5	Intermediate (I)
233	≥ 1	Resistant (R)

235 <sup>c</sup> This interpretive standard is applicable only to agar dilution test with GC agar base and 1% defined  
236 growth supplement.

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

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

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

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

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

261 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also  
262 provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such  
263 standardized procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure  
264 uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to  
265 ciprofloxacin.

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

268 For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*,  
269 and *Neisseria gonorrhoeae*<sup>a</sup>:

	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
270	≥ 21	Susceptible (S)

272	16 – 20	Intermediate	(I)
273	≤ 15	Resistant	(R)

274 <sup>a</sup>These zone diameter standards are applicable only to tests performed for streptococci using Mueller-  
 275 Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.

276 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>b</sup>:

277	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>	
278	≥ 21	Susceptible	(S)

279 <sup>b</sup>This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and  
 280 *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

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

284 For testing *Neisseria gonorrhoeae*<sup>c</sup>:

285	<u>Zone Diameter (mm)</u>	<u>Interpretation</u>	
286	≥ 41	Susceptible	(S)
287	28 – 40	Intermediate	(I)
288	≤ 27	Resistant	(R)

289 <sup>c</sup>This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1%  
 290 defined growth supplement.

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

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

297	<u>Organism</u>		<u>Zone Diameter (mm)</u>
298	<i>E. coli</i>	ATCC 25922	30 – 40
299	<i>H. influenzae</i> <sup>a</sup>	ATCC 49247	34 – 42
300	<i>N. gonorrhoeae</i> <sup>b</sup>	ATCC 49226	48 – 58
301	<i>P. aeruginosa</i>	ATCC 27853	25 – 33
302	<i>S. aureus</i>	ATCC 25923	22 – 30

303 <sup>a</sup> These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using  
 304 *Haemophilus* Test Medium (HTM)<sup>2</sup>.

305 <sup>b</sup> These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC  
 306 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

### 307 **INDICATIONS AND USAGE**

308 CIPRO is indicated for the treatment of infections caused by susceptible strains of the designated  
 309 microorganisms in the conditions and patient populations listed below. Please see **DOSAGE AND**  
 310 **ADMINISTRATION** for specific recommendations.

311

#### 312 **Adult Patients:**

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

315 *diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*,  
316 *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

317 **Acute Uncomplicated Cystitis in females** caused by *Escherichia coli* or *Staphylococcus*  
318 *saprophyticus*.

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

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

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

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

328 **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*,  
329 *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella*  
330 *morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-  
331 susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

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

334 **Complicated Intra-Abdominal Infections** (used in combination with metronidazole) caused by  
335 *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides*  
336 *fragilis*.

337 **Infectious Diarrhea** caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*,  
338 *Shigella boydii*<sup>†</sup>, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei*<sup>†</sup> when antibacterial therapy  
339 is indicated.

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

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

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

344

345 **Pediatric patients (1 to 17 years of age):**

346 **Complicated Urinary Tract Infections and Pyelonephritis** due to *Escherichia coli*.

347 NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric  
348 population due to an increased incidence of adverse events compared to controls, including events  
349 related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use,**  
350 **ADVERSE REACTIONS** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones,  
351 is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile  
352 animals. (See **ANIMAL PHARMACOLOGY**.)

353

354 **Adult and Pediatric Patients:**

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

357 Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably  
358 likely to predict clinical benefit and provide the basis for this indication.<sup>4</sup> (See also,  
359 **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

360 <sup>†</sup>Although treatment of infections due to this organism in this organ system demonstrated a clinically  
361 significant outcome, efficacy was studied in fewer than 10 patients.



362  
363 If anaerobic organisms are suspected of contributing to the infection, appropriate therapy should be  
364 administered. Appropriate culture and susceptibility tests should be performed before treatment in  
365 order to isolate and identify organisms causing infection and to determine their susceptibility to  
366 ciprofloxacin. Therapy with CIPRO may be initiated before results of these tests are known; once  
367 results become available appropriate therapy should be continued. As with other drugs, some strains  
368 of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with  
369 ciprofloxacin. Culture and susceptibility testing performed periodically during therapy will provide  
370 information not only on the therapeutic effect of the antimicrobial agent but also on the possible  
371 emergence of bacterial resistance.

372 To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO Tablets  
373 and CIPRO Oral Suspension and other antibacterial drugs, CIPRO Tablets and CIPRO Oral  
374 Suspension should be used only to treat or prevent infections that are proven or strongly suspected to  
375 be caused by susceptible bacteria. When culture and susceptibility information are available, they  
376 should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local  
377 epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

#### 378 **CONTRAINDICATIONS**

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

#### 381 **WARNINGS**

382 **Pregnant Women: THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN**  
383 **PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.** (See  
384 **PRECAUTIONS: Pregnancy, and Nursing Mothers** subsections.)

385  
386 **Pediatrics:** Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for  
387 infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse  
388 events compared to controls, including events related to joints and/or surrounding tissues, has been  
389 observed. (See **ADVERSE REACTIONS**.)

390  
391 In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature dogs.  
392 Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions  
393 of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing  
394 joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL**  
395 **PHARMACOLOGY**.)

396  
397 **Central Nervous System Disorders:** Convulsions, increased intracranial pressure, and toxic  
398 psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin  
399 may also cause central nervous system (CNS) events including: dizziness, confusion, tremors,  
400 hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following  
401 the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be  
402 discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used  
403 with caution in patients with known or suspected CNS disorders that may predispose to seizures or  
404 lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other  
405 risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy,  
406 renal dysfunction). (See **PRECAUTIONS: General, Information for Patients, Drug Interactions**  
407 and **ADVERSE REACTIONS**.)

408 **Theophylline: SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN**  
409 **PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND**

410 **THEOPHYLLINE.** These reactions have included cardiac arrest, seizure, status epilepticus, and  
411 respiratory failure. Although similar serious adverse effects have been reported in patients receiving  
412 theophylline alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be  
413 eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be monitored  
414 and dosage adjustments made as appropriate.

415 **Hypersensitivity Reactions:** Serious and occasionally fatal hypersensitivity (anaphylactic) reactions,  
416 some following the first dose, have been reported in patients receiving quinolone therapy. Some  
417 reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or  
418 facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity  
419 reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine.  
420 Oxygen, intravenous steroids, and airway management, including intubation, should be administered  
421 as indicated.

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

427 **Pseudomembranous Colitis: Pseudomembranous colitis has been reported with nearly all**  
428 **antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-**  
429 **threatening. Therefore, it is important to consider this diagnosis in patients who present with**  
430 **diarrhea subsequent to the administration of antibacterial agents.**

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

434 After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be  
435 initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In  
436 moderate to severe cases, consideration should be given to management with fluids and electrolytes,  
437 protein supplementation, and treatment with an antibacterial drug clinically effective against *C.*  
438 *difficile colitis*. Drugs that inhibit peristalsis should be avoided.

439 **Tendon Rupture:** Ruptures of the shoulder, hand, and Achilles and other tendon ruptures that  
440 required surgical repair or resulted in prolonged disability have been reported in patients receiving  
441 quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that the risk may be  
442 increased in patients receiving concomitant corticosteroids, especially in the elderly. Ciprofloxacin  
443 should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

444 **Syphilis:** Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial  
445 agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms  
446 of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time  
447 of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis  
448 after three months.

## 449 **PRECAUTIONS**

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

455 **Central Nervous System:** Quinolones, including ciprofloxacin, may also cause central nervous  
456 system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia.  
457 (See **WARNINGS, Information for Patients, and Drug Interactions.**)

458 **Renal Impairment:** Alteration of the dosage regimen is necessary for patients with impairment of  
459 renal function. (See **DOSAGE AND ADMINISTRATION.**)

460 **Phototoxicity:** Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has  
461 been observed in patients who are exposed to direct sunlight while receiving some members of the  
462 quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if  
463 phototoxicity occurs.

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

466 Prescribing CIPRO Tablets and CIPRO Oral Suspension in the absence of a proven or strongly  
467 suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient  
468 and increases the risk of the development of drug-resistant bacteria.

469 **Information for Patients:**

470 Patients should be advised:

- 471 • that antibacterial drugs including CIPRO Tablets and CIPRO Oral Suspension should only be used  
472 to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO  
473 Tablets and CIPRO Oral Suspension is prescribed to treat a bacterial infection, patients should be  
474 told that although it is common to feel better early in the course of therapy, the medication should  
475 be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1)  
476 decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria  
477 will develop resistance and will not be treatable by CIPRO Tablets and CIPRO Oral Suspension or  
478 other antibacterial drugs in the future.
- 479 • that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other  
480 quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or  
481 sucralfate, Videx<sup>®</sup> (didanosine) chewable/buffered tablets or pediatric powder, or with other  
482 products containing calcium, iron or zinc should be avoided. Ciprofloxacin may be taken two hours  
483 before or six hours after taking these products. Ciprofloxacin should not be taken with dairy  
484 products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin  
485 may be significantly reduced; however, ciprofloxacin may be taken with a meal that contains these  
486 products.
- 487 • that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose,  
488 and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- 489 • to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to  
490 discontinue therapy if phototoxicity occurs.
- 491 • to discontinue treatment; rest and refrain from exercise; and inform their physician if they  
492 experience pain, inflammation, or rupture of a tendon.
- 493 • that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how  
494 they react to this drug before they operate an automobile or machinery or engage in activities  
495 requiring mental alertness or coordination.
- 496 • that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of  
497 caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- 498 • that convulsions have been reported in patients receiving quinolones, including ciprofloxacin, and to  
499 notify their physician before taking this drug if there is a history of this condition.

500 • that ciprofloxacin has been associated with an increased rate of adverse events involving joints and  
501 surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents  
502 should inform their child's physician if the child has a history of joint-related problems before  
503 taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-  
504 related problems that occur during or following ciprofloxacin therapy. (See **WARNINGS**,  
505 **PRECAUTIONS, Pediatric Use** and **ADVERSE REACTIONS**.)

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

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

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

518 Histamine H<sub>2</sub>-receptor antagonists appear to have no significant effect on the bioavailability of  
519 ciprofloxacin.

520 Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving  
521 concomitant ciprofloxacin.

522 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare  
523 occasions, resulted in severe hypoglycemia.

524 Some quinolones, including ciprofloxacin, have been associated with transient elevations in serum  
525 creatinine in patients receiving cyclosporine concomitantly.

526 Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral  
527 anticoagulant warfarin or its derivatives. When these products are administered concomitantly,  
528 prothrombin time or other suitable coagulation tests should be closely monitored.

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

532 Renal tubular transport of methotrexate may be inhibited by concomitant administration of  
533 ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the  
534 risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should  
535 be carefully monitored when concomitant ciprofloxacin therapy is indicated.

536 Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time  
537 to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of  
538 ciprofloxacin.

539 Animal studies have shown that the combination of very high doses of quinolones and certain non-  
540 steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

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

543 Salmonella/Microsome Test (Negative)  
544 *E. coli* DNA Repair Assay (Negative)

545 Mouse Lymphoma Cell Forward Mutation Assay (Positive)  
546 Chinese Hamster V<sub>79</sub> Cell HGPRT Test (Negative)  
547 Syrian Hamster Embryo Cell Transformation Assay (Negative)  
548 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)  
549 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)  
550 Rat Hepatocyte DNA Repair Assay (Positive)

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

553 Rat Hepatocyte DNA Repair Assay  
554 Micronucleus Test (Mice)  
555 Dominant Lethal Test (Mice)

556 Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects  
557 due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively  
558 (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>).

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

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

570 Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (approximately 0.7-  
571 times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>) revealed no evidence of  
572 impairment.

#### 573 **Pregnancy: Teratogenic Effects. Pregnancy Category C:**

574 There are no adequate and well-controlled studies in pregnant women. An expert review of published  
575 data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information  
576 System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial  
577 teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no  
578 risk.<sup>7</sup>

579 A controlled prospective observational study followed 200 women exposed to fluoroquinolones  
580 (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.<sup>8</sup> In utero  
581 exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major  
582 malformations. The reported rates of major congenital malformations were 2.2% for the  
583 fluoroquinolone group and 2.6% for the control group (background incidence of major malformations  
584 is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the  
585 groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in  
586 the ciprofloxacin exposed children.

587 Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure  
588 (93% first trimester exposures).<sup>9</sup> There were 70 ciprofloxacin exposures, all within the first trimester.  
589 The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones  
590 overall were both within background incidence ranges. No specific patterns of congenital

591 abnormalities were found. The study did not reveal any clear adverse reactions due to in utero  
592 exposure to ciprofloxacin.

593 No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women  
594 exposed to ciprofloxacin during pregnancy.<sup>7,8</sup> However, these small postmarketing epidemiology  
595 studies, of which most experience is from short term, first trimester exposure, are insufficient to  
596 evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the  
597 safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be  
598 used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother  
599 (see **WARNINGS**).

600 Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and  
601 0.3 times the maximum daily human dose based upon body surface area, respectively) and have  
602 revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, oral ciprofloxacin dose  
603 levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic  
604 dose based upon mg/m<sup>2</sup>) produced gastrointestinal toxicity resulting in maternal weight loss and an  
605 increased incidence of abortion, but no teratogenicity was observed at either dose level. After  
606 intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest  
607 recommended therapeutic dose based upon mg/m<sup>2</sup>) no maternal toxicity was produced and no  
608 embryotoxicity or teratogenicity was observed. (See **WARNINGS**.)

609 **Nursing Mothers:** Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed  
610 by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants  
611 nursing from mothers taking ciprofloxacin, a decision should be made whether to discontinue nursing  
612 or to discontinue the drug, taking into account the importance of the drug to the mother.

613 **Pediatric Use:** Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in  
614 weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL**  
615 **PHARMACOLOGY**.)

#### 616 *Inhalational Anthrax (Post-Exposure)*

617 Ciprofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-  
618 benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate.  
619 For information regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE**  
620 **AND ADMINISTRATION** and **INHALATIONAL ANTHRAX – ADDITIONAL**  
621 **INFORMATION**.

622

#### 623 *Complicated Urinary Tract Infection and Pyelonephritis*

624 Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis  
625 due to *Escherichia coli*. Although effective in clinical trials, ciprofloxacin is not a drug of first choice  
626 in the pediatric population due to an increased incidence of adverse events compared to the controls,  
627 including events related to joints and/or surrounding tissues. The rates of these events in pediatric  
628 patients with complicated urinary tract infection and pyelonephritis within six weeks of follow-up  
629 were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at  
630 any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate  
631 of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the  
632 ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS**  
633 and **CLINICAL STUDIES**.)

#### 634 *Cystic Fibrosis*

635 Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a  
636 randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic  
637 fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one

638 week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62  
639 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3  
640 mg/kg/dose q8h for a total of 10-21 days. Patients less than 5 years of age were not studied. Safety  
641 monitoring in the study included periodic range of motion examinations and gait assessments by  
642 treatment-blinded examiners. Patients were followed for an average of 23 days after completing  
643 treatment (range 0-93 days). This study was not designed to determine long term effects and the safety  
644 of repeated exposure to ciprofloxacin.

645 Musculoskeletal adverse events in patients with cystic fibrosis were reported in 22% of the patients in  
646 the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in  
647 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was  
648 reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other  
649 adverse events were similar in nature and frequency between treatment arms. One of sixty-seven  
650 patients developed arthritis of the knee nine days after a ten day course of treatment with  
651 ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other  
652 abnormalities eight months after treatment. However, the relationship of this event to the patient's  
653 course of ciprofloxacin can not be definitively determined, particularly since patients with cystic  
654 fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

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

## 667 **ADVERSE REACTIONS**

668 **Adverse Reactions in Adult Patients:** During clinical investigations with oral and parenteral  
669 ciprofloxacin, 49,038 patients received courses of the drug. Most of the adverse events reported were  
670 described as only mild or moderate in severity, abated soon after the drug was discontinued, and  
671 required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.0% of orally  
672 treated patients.

673 The most frequently reported drug related events, from clinical trials of all formulations, all dosages,  
674 all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%),  
675 diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

676 Additional medically important events that occurred in less than 1% of ciprofloxacin patients are  
677 listed below.

678 **BODY AS A WHOLE:** headache, abdominal pain/discomfort, foot pain, pain, pain in extremities,  
679 injection site reaction (ciprofloxacin intravenous)

680 **CARDIOVASCULAR:** palpitation, atrial flutter, ventricular ectopy, syncope, hypertension,  
681 angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis,  
682 tachycardia, migraine, hypotension

683 **CENTRAL NERVOUS SYSTEM:** restlessness, dizziness, lightheadedness, insomnia, nightmares,  
684 hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy,

685 drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia,  
686 abnormal gait, grand mal convulsion  
687 GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation,  
688 gastrointestinal bleeding, cholestatic jaundice, hepatitis  
689 HEMIC/LYMPHATIC: lymphadenopathy, petechia  
690 METABOLIC/NUTRITIONAL: amylase increase, lipase increase  
691 MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare  
692 up of gout  
693 RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention,  
694 urethral bleeding, vaginitis, acidosis, breast pain  
695 RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis,  
696 bronchospasm, pulmonary embolism  
697 SKIN/HYPERSENSITIVITY: allergic reaction, pruritus, urticaria, photosensitivity, flushing,  
698 fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous  
699 candidiasis, hyperpigmentation, erythema nodosum, sweating  
700 SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness  
701 of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste,  
702 chromatopsia

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

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

710 **Adverse Reactions in Pediatric Patients:** Ciprofloxacin, administered I.V. and /or orally, was  
711 compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or  
712 pyelonephritis in pediatric patients 1 to 17 years of age (mean age of  $6 \pm 4$  years). The trial was  
713 conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The  
714 duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88  
715 days). The primary objective of the study was to assess musculoskeletal and neurological safety  
716 within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349  
717 comparator-treated patients enrolled.

718  
719 An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse  
720 events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-  
721 emergent). These events were evaluated in a comprehensive fashion and included such conditions as  
722 arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain,  
723 pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee,  
724 elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events  
725 were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated  
726 patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events  
727 occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of  
728 end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events.  
729 The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless  
730 of whether they received I.V. or oral therapy. Ciprofloxacin-treated patients were more likely to  
731 report more than one event and on more than one occasion compared to control patients. These events  
732 occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared  
733 to the control group. At the end of 1 year, the rate of these events reported at any time during that



734 period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-  
735 treated patients.

736  
737 An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An  
738 MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse  
739 syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be  
740 excluded. The patient recovered by 4 months without surgical intervention.

741  
742  
743

#### Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC

	Ciprofloxacin	Comparator
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval*	(-0.8%, +7.2%)	
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2%)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, +9.1%)	

744

745 \*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that  
746 of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence  
747 interval indicated that it could not be concluded that ciprofloxacin group had findings comparable to the control  
748 group.

749

750 The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in  
751 the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness,  
752 nervousness, insomnia, and somnolence.

753

754 In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and  
755 within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31%  
756 (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of  
757 ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were  
758 seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients.  
759 Discontinuation of drug due to an adverse events were observed in 3% (10/335) of ciprofloxacin-  
760 treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at  
761 least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%,  
762 accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and  
763 rash 1.8%.

764

765 In addition to the events reported in pediatric patients in clinical trials, it should be expected that  
766 events reported in adults during clinical trials or post-marketing experience may also occur in  
767 pediatric patients.

768

769 **Post-Marketing Adverse Events:** The following adverse events have been reported from worldwide  
770 marketing experience with quinolones, including ciprofloxacin. Because these events are reported  
771 voluntarily from a population of uncertain size, it is not always possible to reliably estimate their  
772 frequency or establish a causal relationship to drug exposure. Decisions to include these events in  
773 labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2)  
774 frequency of the reporting, or (3) strength of causal connection to the drug.

775 Agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol  
776 elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme,  
777 exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic  
778 failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice,  
779 marrow depression (life threatening), methemoglobinemia, monoliasis (oral, gastrointestinal, vaginal)  
780 myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis,  
781 pancytopenia (life threatening or fatal outcome), phenytoin alteration (serum), potassium elevation  
782 (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of  
783 pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis  
784 (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis,  
785 tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal  
786 candidiasis, and vasculitis. (See **PRECAUTIONS.**)

787 **Adverse Laboratory Changes:** Changes in laboratory parameters listed as adverse events without  
788 regard to drug relationship are listed below:

789 Hepatic – Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%), alkaline phosphatase  
790 (0.8%), LDH (0.4%), serum bilirubin (0.3%).

791 Hematologic – Eosinophilia (0.6%), leukopenia (0.4%), decreased blood platelets (0.1%), elevated  
792 blood platelets (0.1%), pancytopenia (0.1%).

793 Renal – Elevations of serum creatinine (1.1%), BUN (0.9%), **CRYSTALLURIA,**  
794 **CYLINDRURIA, AND HEMATURIA HAVE BEEN REPORTED.**

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

#### 798 **OVERDOSAGE**

799 In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The  
800 stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully  
801 observed and given supportive treatment, including monitoring of renal function and administration of  
802 magnesium, aluminum, or calcium containing antacids which can reduce the absorption of  
803 ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%)  
804 is removed from the body after hemodialysis or peritoneal dialysis.

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

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

#### 813 **DOSAGE AND ADMINISTRATION - ADULTS**

814 CIPRO Tablets and Oral Suspension should be administered orally to adults as described in the  
815 Dosage Guidelines table.

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

819 The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days;  
 820 however, for severe and complicated infections more prolonged therapy may be required.  
 821 Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum  
 822 antacids, or sucralfate, Videx<sup>®</sup> (didanosine) chewable/buffered tablets or pediatric powder for oral  
 823 solution, or other products containing calcium, iron or zinc.

824

**ADULT DOSAGE GUIDELINES**

Infection	Severity	Dose	Frequency	Usual Durations <sup>†</sup>
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 Prostatitis	Mild/Moderate	500 mg	q 12 h	28 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
Acute Sinusitis	Mild/Moderate	500 mg	q 12 h	10 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
Intra-Abdominal*	Complicated	500 mg	q 12 h	7 to 14 Days
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)**		500 mg	q 12 h	60 Days

846

847

\* used in conjunction with metronidazole

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

\*\* 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, reasonably likely to predict clinical benefit.<sup>4</sup> For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

855 **Conversion of I.V. to Oral Dosing in Adults:** Patients whose therapy is started with CIPRO I.V.  
 856 may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of  
 857 the physician (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing  
 858 regimens).

### Equivalent AUC Dosing Regimens

	<u>Cipro Oral Dosage</u>	<u>Equivalent Cipro I.V. Dosage</u>
859		
860		
861	250 mg Tablet q 12 h	200 mg I.V. q 12 h
862	500 mg Tablet q 12 h	400 mg I.V. q 12 h
863	750 mg Tablet q 12 h	400 mg I.V. q 8 h

864 **Adults with Impaired Renal Function:** Ciprofloxacin is eliminated primarily by renal excretion;  
865 however, the drug is also metabolized and partially cleared through the biliary system of the liver and  
866 through the intestine. These alternative pathways of drug elimination appear to compensate for the  
867 reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage  
868 is recommended, particularly for patients with severe renal dysfunction. The following table provides  
869 dosage guidelines for use in patients with renal impairment:

#### RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

870	<b>Creatinine Clearance (mL/min)</b>	<b>Dose</b>
871		
872		
873	> 50	See Usual Dosage.
874	30 – 50	250 – 500 mg q 12 h
875	5 – 29	250 – 500 mg q 18 h
876	Patients on hemodialysis	250–500 mg q 24 h (after dialysis)
877	or Peritoneal dialysis)	

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

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

881  
882 Women: 0.85 x the value calculated for men.

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

884 In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be  
885 administered at the intervals noted above. Patients should be carefully monitored.

#### DOSAGE AND ADMINISTRATION - PEDIATRICS

886  
887 CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage  
888 Guidelines table. An increased incidence of adverse events compared to controls, including events  
889 related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** and  
890 **CLINICAL STUDIES**.)  
891

892  
893 Dosing and initial route of therapy (i.e., I.V. or oral) for complicated urinary tract infection or  
894 pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric  
895 patients with moderate to severe infection were initiated on 6 to 10 mg/kg I.V. every 8 hours and  
896 allowed to switch to oral therapy (10 to 20 mg/kg every 12 hours), at the discretion of the physician.

<b>PEDIATRIC DOSAGE GUIDELINES</b>				
Infection	Route of Administration	Dose (mg/kg)	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis  (patients from 1 to 17 years of age)	Intravenous	6 to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 8 hours	10-21 days*
	Oral	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 12 hours	
Inhalational Anthrax (Post-Exposure)**	Intravenous	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
	Oral	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	

898 \* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was  
899 determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).

900 \*\* Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus*  
901 *anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved  
902 in humans, reasonably likely to predict clinical benefit.<sup>4</sup> For a discussion of ciprofloxacin serum concentrations  
903 in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

904

905 Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of  
906 complicated urinary tract infection and pyelonephritis. No information is available on dosing  
907 adjustments necessary for pediatric patients with moderate to severe renal insufficiency (i.e.,  
908 creatinine clearance of < 50 mL/min/1.73m<sup>2</sup>).

909

910

### HOW SUPPLIED

911 CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-coated  
912 tablets containing 100 mg or 250 mg ciprofloxacin. The 100 mg tablet is coded with the word  
913 “CIPRO” on one side and “100” on the reverse side. The 250 mg tablet is coded with the word  
914 “CIPRO” on one side and “250” on the reverse side. CIPRO is also available as capsule shaped,  
915 slightly yellowish film-coated tablets containing 500 mg or 750 mg ciprofloxacin. The 500 mg tablet  
916 is coded with the word “CIPRO” on one side and “500” on the reverse side. The 750 mg tablet is  
917 coded with the word “CIPRO” on one side and “750” on the reverse side. CIPRO 250 mg, 500 mg,  
918 and 750 mg are available in bottles of 50, 100, and Unit Dose packages of 100. The 100 mg strength is  
919 available only as CIPRO Cystitis pack containing 6 tablets for use only in female patients with acute  
920 uncomplicated cystitis.

921

922

923

924

	<b>Strength</b>	<b>NDC Code</b>	<b>Tablet Identification</b>
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

925	Unit Dose			
926	Package of 100:	250 mg	NDC 0026-8512-48	CIPRO 250
927		500 mg	NDC 0026-8513-48	CIPRO 500
928		750 mg	NDC 0026-8514-48	CIPRO 750
929	Cystitis			
930	Package of 6:	100 mg	NDC 0026-8511-06	CIPRO 100

931 **Store below 30°C (86°F).**

932 CIPRO Oral Suspension is supplied in 5% and 10% strengths. The drug product is composed of two  
 933 components (microcapsules containing the active ingredient and diluent) which must be mixed by the  
 934 pharmacist. See Instructions To The Pharmacist For Use/Handling.

935	Strengths	Total volume after reconstitution	Ciprofloxacin Concentration	Ciprofloxacin contents per bottle	NDC Code
936	5%	100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
937	10%	100 mL	500 mg/5 mL	10,000 mg	0026-8553-36

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

940 **Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing.** A  
 941 teaspoon is provided for the patient.

#### 942 **ANIMAL PHARMACOLOGY**

943 Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of  
 944 most species tested. (See **WARNINGS**.) Damage of weight bearing joints was observed in juvenile  
 945 dogs and rats. In young beagles, 100 mg/kg ciprofloxacin, given daily for 4 weeks, caused  
 946 degenerative articular changes of the knee joint. At 30 mg/kg, the effect on the joint was minimal. In  
 947 a subsequent study in young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg  
 948 ciprofloxacin (approximately 1.3- and 3.5-times the pediatric dose based upon comparative plasma  
 949 AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology  
 950 after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose  
 951 based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not  
 952 associated with arthrototoxicity after an additional treatment-free period of 5 months. In another study,  
 953 removal of weight bearing from the joint reduced the lesions but did not totally prevent them.

954 Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed  
 955 with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacin under alkaline  
 956 conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human  
 957 urine is typically acidic. In rhesus monkeys, crystalluria without nephropathy was noted after single  
 958 oral doses as low as 5 mg/kg (approximately 0.07-times the highest recommended therapeutic dose  
 959 based upon mg/m<sup>2</sup>). After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological  
 960 changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same  
 961 duration (approximately 0.2-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>).

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

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

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

## CLINICAL STUDIES

### Complicated Urinary Tract Infection and Pyelonephritis – Efficacy in Pediatric Patients:

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.

Ciprofloxacin, administered I.V. and /or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) and pyelonephritis in pediatric patients 1 to 17 years of age (mean age of  $6 \pm 4$  years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety.

Patients were evaluated for clinical success and bacteriological eradication of the baseline organism(s) with no new infection or superinfection at 5 to 9 days post-therapy (Test of Cure or TOC). The Per Protocol population had a causative organism(s) with protocol specified colony count(s) at baseline, no protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population were similar between ciprofloxacin and the comparator group as shown below.

#### Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	CIPRO	Comparator
Randomized Patients	337	352
Per Protocol Patients	211	231
Clinical Response at 5 to 9 Days Post-Treatment	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]		
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [ -1.3%, 13.1%]		
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
<i>Escherichia coli</i>	156/178 (88%)	161/179 (90%)

\* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.

### INHALATIONAL ANTHRAX IN ADULTS AND PEDIATRICS – ADDITIONAL INFORMATION

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady-state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 µg/mL. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma

1005 concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL,  
 1006 following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the  
 1007 second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak  
 1008 concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on  
 1009 cartilage, following the administration of ciprofloxacin to pediatric patients are limited. (For  
 1010 additional information, see **PRECAUTIONS, Pediatric Use**.) Ciprofloxacin serum concentrations  
 1011 achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and  
 1012 provide the basis for this indication.<sup>4</sup>

1013 A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD<sub>50</sub>  
 1014 (~5.5 x 10<sup>5</sup> spores (range 5-30 LD<sub>50</sub>) of *B. anthracis* was conducted. The minimal inhibitory  
 1015 concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the  
 1016 animals studied, mean serum concentrations of ciprofloxacin achieved at expected T<sub>max</sub> (1 hour post-  
 1017 dose) following oral dosing to steady-state ranged from 0.98 to 1.69 µg/mL. Mean steady-state trough  
 1018 concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL<sup>5</sup>. Mortality due to anthrax for  
 1019 animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was  
 1020 significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin-  
 1021 treated animal that died of anthrax did so following the 30-day drug administration period.<sup>6</sup>

1022 **Instructions To The Pharmacist For Use/Handling Of CIPRO Oral Suspension:**

1023 CIPRO Oral Suspension is supplied in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin  
 1024 in 100 mL) strengths. The drug product is composed of two components (microcapsules and diluent)  
 1025 which must be combined prior to dispensing.

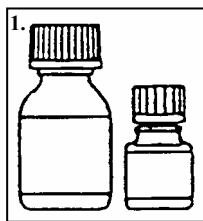
1026 One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250 mg of ciprofloxacin.

1027 One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500 mg of ciprofloxacin.

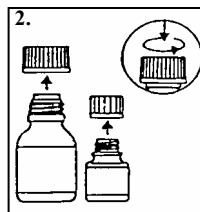
1028 **Appropriate Dosing Volumes of the Oral Suspensions:**

1029	<u>Dose</u>	<u>5%</u>	<u>10%</u>
1030	250 mg	5 mL	2.5 mL
1031	500 mg	10 mL	5 mL
1032	750 mg	15 mL	7.5 mL

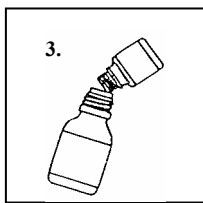
1033 **Preparation of the suspension:**



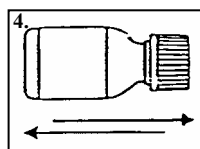
1034 1. The small bottle  
 1035 contains the  
 1036 microcapsules, the  
 1037 large bottle contains  
 1038 the diluent.



1039 2. Open both bottles.  
 1040 Child-proof cap: Press  
 1041 down according to  
 1042 instructions on the cap  
 1043 while turning to the left.



1044 3. Pour the  
 1045 microcapsules  
 1046 completely into the  
 larger bottle of  
 diluent. **Do not add  
 water to the  
 suspension.**



4. Remove the top layer of  
 the diluent bottle label  
 (to reveal the CIPRO  
 Oral Suspension label).  
 Close the large bottle  
 completely according to  
 the directions on the cap  
 and shake vigorously for  
 about 15 seconds. The  
 suspension is ready for  
 use.



1047 **CIPRO Oral Suspension should not be administered through feeding tubes due to its physical**  
1048 **characteristics.**

1049 **Instruct the patient to shake CIPRO Oral Suspension vigorously each time before use for**  
1050 **approximately 15 seconds and not to chew the microcapsules.**

1051

1052 **References:**

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1072

1073

**Patient Information About:**

1074

**CIPRO®**

1075

**(ciprofloxacin hydrochloride) TABLETS**

1076

**CIPRO®**

1077

**(ciprofloxacin\*) ORAL SUSPENSION**

1078 This section contains important patient information about CIPRO (ciprofloxacin hydrochloride)  
1079 Tablets and CIPRO (ciprofloxacin\*) Oral Suspension and should be read completely before you begin  
1080 treatment. This section does not take the place of discussion with your doctor or health care  
1081 professional about your medical condition or your treatment. This section does not list all benefits and  
1082 risks of CIPRO. If you have any concerns about your condition or your medicine, ask your doctor.  
1083 Only your doctor can determine if CIPRO is right for you.

1084 **What is CIPRO?**

1085 CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung, sinus,  
1086 bone, and skin infections caused by certain germs called bacteria. CIPRO kills many types of bacteria  
1087 that can infect these areas of the body. CIPRO has been shown in a large number of clinical trials to  
1088 be safe and effective for the treatment of bacterial infections.

1089 Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common  
1090 cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your doctor if your  
1091 condition is not improving while taking CIPRO.

1092 CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500 mg and  
1093 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is available in  
1094 concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).

1095 **How and when should I take CIPRO?**

1096 **CIPRO Tablets:**

1097 Unless directed otherwise by your physician, CIPRO should be taken twice a day at approximately the  
1098 same time, in the morning and in the evening. CIPRO can be taken with food or on an empty stomach.  
1099 CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone;  
1100 however, CIPRO may be taken with a meal that contains these products.

1101 You should take CIPRO for as long as your doctor prescribes it, even after you start to feel better.  
1102 Stopping an antibiotic too early may result in failure to cure your infection. Do not take a double dose  
1103 of CIPRO even if you miss a dose by mistake.

1104 **CIPRO Oral Suspension:**

1105 Take CIPRO Oral Suspension in the same way as above. In addition, remember to **shake the bottle**  
1106 **vigorously each time before use for approximately 15 seconds** to make sure the suspension is  
1107 mixed well. Be sure to swallow the required amount of suspension. Do not chew the microcapsules.  
1108 Close the bottle completely after use. The product can be used for 14 days when stored in a  
1109 refrigerator or at room temperature. After treatment has been completed, any remaining suspension  
1110 should be discarded.

1111 **Who should not take CIPRO?**

1112 You should not take CIPRO if you have ever had a severe reaction to any of the group of antibiotics  
1113 known as “quinolones”.

1114 CIPRO is not recommended during pregnancy or nursing, as the effects of CIPRO on the unborn child  
1115 or nursing infant are unknown. If you are pregnant or plan to become pregnant while taking CIPRO  
1116 talk to your doctor before taking this medication.

1117 Due to possible side effects, CIPRO is not recommended for persons less than 18 years of age except  
1118 for specific serious infections, such as complicated urinary tract infections.

1119 **What are the possible side effects of CIPRO?**

1120 CIPRO is generally well tolerated. The most common side effects, which are usually mild, include  
1121 nausea, diarrhea, vomiting, and abdominal pain/discomfort. If diarrhea persists, call your health care  
1122 professional.

1123 Rare cases of allergic reactions have been reported in patients receiving quinolones, including CIPRO,  
1124 even after just one dose. If you develop hives, difficulty breathing, or other symptoms of a severe  
1125 allergic reaction, seek emergency treatment right away. If you develop a skin rash, you should stop  
1126 taking CIPRO and call your health care professional.

1127 Some patients taking quinolone antibiotics may become more sensitive to sunlight or ultraviolet light  
1128 such as that used in tanning salons. You should avoid excessive exposure to sunlight or ultraviolet  
1129 light while you are taking CIPRO.

1130 You should be careful about driving or operating machinery until you are sure CIPRO is not causing  
1131 dizziness. Convulsions have been reported in patients receiving quinolone antibiotics including  
1132 ciprofloxacin. Be sure to let your physician know if you have a history of convulsions. Quinolones,  
1133 including ciprofloxacin, have been rarely associated with other central nervous system events  
1134 including confusion, tremors, hallucinations, and depression.

1135 CIPRO has been rarely associated with inflammation of tendons. If you experience pain, swelling or  
1136 rupture of a tendon, you should stop taking CIPRO and call your health care professional.

1137 CIPRO has been associated with an increased rate of side effects with joints and surrounding  
1138 structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their  
1139 child's physician if the child has a history of joint-related problems before taking this drug. Parents of  
1140 pediatric patients should also notify their child's physician of any joint related problems that occur  
1141 during or following CIPRO therapy.

1142 If you notice any side effects not mentioned in this section, or if you have any concerns about side  
1143 effects you may be experiencing, please inform your health care professional.

1144 **What about other medications I am taking?**

1145 CIPRO can affect how other medicines work. Tell your doctor about all other prescription and non-  
1146 prescription medicines or supplements you are taking. This is especially important if you are taking  
1147 theophylline. Other medications including warfarin, glyburide, and phenytoin may also interact with  
1148 CIPRO.

1149 Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium,  
1150 aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from working.  
1151 Other medications such as sulcrafate and Videx<sup>®</sup> (didanosine) chewable/buffered tablets or pediatric  
1152 powder may also stop CIPRO from working. You should take CIPRO either 2 hours before or 6 hours  
1153 after taking these products.

1154 **What if I have been prescribed CIPRO for possible anthrax exposure?**

1155 CIPRO has been approved to reduce the chance of developing anthrax infection following exposure to  
1156 the anthrax bacteria. In general, CIPRO is not recommended for children; however, it is approved for  
1157 use in patients younger than 18 years old for anthrax exposure. If you are pregnant, or plan to become  
1158 pregnant while taking CIPRO, you and your doctor should discuss if the benefits of taking CIPRO for  
1159 anthrax outweigh the risks.

1160 CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent anthrax  
1161 might be acceptable due to the seriousness of the disease. You and your doctor should discuss the  
1162 risks of not taking your medicine against the risks of experiencing side effects.

1163 CIPRO can cause dizziness, confusion, or other similar side effects in some people. Therefore, it is  
1164 important to know how CIPRO affects you before driving a car or performing other activities that  
1165 require you to be alert and coordinated such as operating machinery.

1166 Your doctor has prescribed CIPRO only for you. Do not give it to other people. Do not use it for a  
1167 condition for which it was not prescribed. You should take your CIPRO for as long as your doctor  
1168 prescribes it; stopping CIPRO too early may result in failure to prevent anthrax.

1169 **Remember:**

1170 Do not give CIPRO to anyone other than the person for whom it was prescribed.

1171 Take your dose of CIPRO in the morning and in the evening.

1172 Complete the course of CIPRO even if you are feeling better.

1173 Keep CIPRO and all medications out of reach of children.

1174 \* Does not comply with USP with regards to "loss on drying" and "residue on ignition".

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**Bayer HealthCare**

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Bayer Pharmaceuticals Corporation  
400 Morgan Lane  
West Haven, CT 06516

1182 **Rx Only**

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1186 CIPRO (ciprofloxacin\*) 5% and 10% Oral Suspension Made in Italy.

1187 CIPRO (ciprofloxacin HCl) Tablets Made in U.S.A. and Germany

**CIPRO<sup>®</sup> I.V.**  
**(ciprofloxacin)**  
**For Intravenous Infusion**

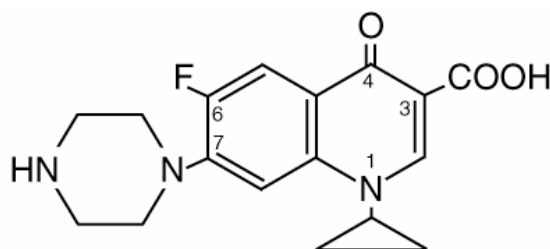
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3/25/04

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO IV and other antibacterial drugs, CIPRO IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

**DESCRIPTION**

CIPRO<sup>®</sup> I.V. (ciprofloxacin) is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is C<sub>17</sub>H<sub>18</sub>FN<sub>3</sub>O<sub>3</sub> and its chemical structure is:



Ciprofloxacin is a faint to light yellow crystalline powder with a molecular weight of 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol. CIPRO I.V. solutions are available as sterile 1.0% aqueous concentrates, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulas contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrates in vials is 3.3 to 3.9. The pH range for the 0.2% ready-for-use infusion solutions is 3.5 to 4.6.

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

**CLINICAL PHARMACOLOGY**

**Absorption**

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

**Steady-state Ciprofloxacin Serum Concentrations (mg/mL)**  
**After 60-minute I.V. Infusions q 12 h.**

Dose	Time after starting the infusion					
	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

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. 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.

The absolute bioavailability of oral ciprofloxacin is within a range of 70–80% with no substantial loss by first pass metabolism. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500-mg oral dose given every 12 hours. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750-mg oral dose given every 12 hours. A 400-mg I.V. dose results in a  $C_{max}$  similar to that observed with a 750-mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250-mg oral dose given every 12 hours.

<b>Steady-state Pharmacokinetic Parameter Following Multiple Oral and I.V. Doses</b>				
Parameters	500 mg q12h, P.O.	400 mg q12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC ( $\mu\text{g}\cdot\text{hr}/\text{mL}$ )	13.7 <sup>a</sup>	12.7 <sup>a</sup>	31.6 <sup>b</sup>	32.9 <sup>c</sup>
$C_{max}$ ( $\mu\text{g}/\text{mL}$ )	2.97	4.56	3.59	4.07

<sup>a</sup> AUC<sub>0-12h</sub>

<sup>b</sup> AUC 24h=AUC<sub>0-12h</sub> × 2

<sup>c</sup> AUC 24h=AUC<sub>0-8h</sub> × 3

### Distribution

After intravenous administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous chambers of the eye are lower than in serum.

### Metabolism

After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The binding of ciprofloxacin to serum proteins is 20 to 40%.

### Excretion

The serum elimination half-life is approximately 5–6 hours and the total clearance is around 35 L/hr. 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  $\mu\text{g}/\text{mL}$  0–2 hours after dosing and are generally greater than 15  $\mu\text{g}/\text{mL}$  8–12 hours after dosing. Following a 400-mg I.V. dose, urine concentrations generally exceed 400  $\mu\text{g}/\text{mL}$  0–2 hours after dosing and are usually greater than 30  $\mu\text{g}/\text{mL}$  8–12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (<1%) is recovered from the bile as unchanged drug. Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing.

### Special Populations

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

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

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

Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean  $C_{max}$  was 2.4 mg/L (range: 1.5 – 3.4 mg/L) and the mean AUC was 9.2 mg\*h/L (range: 5.8 – 14.9

mg\*h/L). There was no apparent age-dependence, and no notable increase in C<sub>max</sub> or AUC upon multiple dosing (10 mg/kg TID). In children with severe sepsis who were given intravenous ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C<sub>max</sub> was 6.1 mg/L (range: 4.6 – 8.3 mg/L) in 10 children less than 1 year of age; and 7.2 mg/L (range: 4.7 – 11.8 mg/L) in 10 children between 1 and 5 years of age. The AUC values were 17.4 mg\*h/L (range: 11.8 – 32.0 mg\*h/L) and 16.5 mg\*h/L (range: 11.0 – 23.8 mg\*h/L) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4 - 5 hours, and the bioavailability of the oral suspension is approximately 60%.

**Drug-drug Interactions:** The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporins, phenytoin, sulfonyleurea glyburide, metronidazole, warfarin, probenecid, and piperacillin sodium has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

**Microbiology:** Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations.

Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

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

**Aerobic gram-positive microorganisms**

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

*Staphylococcus aureus* (methicillin-susceptible strains only)

*Staphylococcus epidermidis* (methicillin-susceptible strains only)

*Staphylococcus saprophyticus*

*Streptococcus pneumoniae* (penicillin-susceptible strains)

*Streptococcus pyogenes*

**Aerobic gram-negative microorganisms**

*Citrobacter diversus*

*Citrobacter freundii*

*Enterobacter cloacae*

*Escherichia coli*

*Haemophilus influenzae*

*Haemophilus parainfluenzae*

*Klebsiella pneumoniae*

*Moraxella catarrhalis*

*Morganella morganii*

*Proteus mirabilis*

*Proteus vulgaris*

*Providencia rettgeri*

*Providencia stuartii*

*Pseudomonas aeruginosa*

*Serratia marcescens*

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

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

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

**Aerobic gram-positive microorganisms**

*Staphylococcus haemolyticus*

*Staphylococcus hominis*

*Streptococcus pneumoniae* (penicillin-resistant strains)

### Aerobic gram-negative microorganisms

<i>Acinetobacter lwoffii</i>	<i>Salmonella typhi</i>
<i>Aeromonas hydrophila</i>	<i>Shigella boydii</i>
<i>Campylobacter jejuni</i>	<i>Shigella dysenteriae</i>
<i>Edwardsiella tarda</i>	<i>Shigella flexneri</i>
<i>Enterobacter aerogenes</i>	<i>Shigella sonnei</i>
<i>Klebsiella oxytoca</i>	<i>Vibrio cholerae</i>
<i>Legionella pneumophila</i>	<i>Vibrio parahaemolyticus</i>
<i>Neisseria gonorrhoeae</i>	<i>Vibrio vulnificus</i>
<i>Pasteurella multocida</i>	<i>Yersinia enterocolitica</i>
<i>Salmonella enteritidis</i>	

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

### Susceptibility Tests

**Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method<sup>1</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of ciprofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*<sup>a</sup>:

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

<sup>a</sup> These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>b</sup>:

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

<sup>b</sup> This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium<sup>1</sup>.

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

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> <sup>a</sup>	ATCC 49247	0.004 – 0.03
<i>P. aeruginosa</i>	ATCC 27853	0.25 – 1.0



*S. aureus*

ATCC 29213

0.12 – 0.5

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

**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 procedure<sup>2</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-mg 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-mg ciprofloxacin disk should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenzae*, and *Haemophilus parainfluenzae*<sup>a</sup>:

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

<sup>a</sup> These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO<sub>2</sub>.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*<sup>b</sup>:

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

<sup>b</sup> This zone diameter standard is applicable only to tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

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

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

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> <sup>a</sup>	ATCC 49247	34-42
<i>P. aeruginosa</i>	ATCC 27853	25-33
<i>S. aureus</i>	ATCC 25923	22-30

<sup>a</sup> These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)<sup>2</sup>.

## INDICATIONS AND USAGE

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

### Adult Patients:

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

**Lower Respiratory Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae* subspecies *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*.

**Nosocomial Pneumonia** caused by *Haemophilus influenzae* or *Klebsiella pneumoniae*.

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

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

**Complicated Intra-Abdominal Infections** (used in conjunction with metronidazole) caused by *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or *Bacteroides fragilis*.

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

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

**Empirical Therapy for Febrile Neutropenic Patients** in combination with piperacillin sodium. (See **CLINICAL STUDIES**.)

**Pediatric patients (1 to 17 years of age):**

**Complicated Urinary Tract Infections and Pyelonephritis** due to *Escherichia coli*.

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS, Pediatric Use, ADVERSE REACTIONS** and **CLINICAL STUDIES**.) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY**.)

**Adult and Pediatric Patients:**

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

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

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

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

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

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO IV and other antibacterial drugs, CIPRO IV should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

#### **CONTRAINDICATIONS**

CIPRO I.V. (ciprofloxacin) is contraindicated in persons with history of hypersensitivity to ciprofloxacin or any member of the quinolone class of antimicrobial agents.

#### **WARNINGS**

**Pregnant Women: THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.** (See **PRECAUTIONS: Pregnancy, and Nursing Mothers** subsections.)

**Pediatrics:** Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS**.) In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

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

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

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

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

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

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

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile colitis*. Drugs that inhibit peristalsis should be avoided.

**Tendon Rupture:** Ruptures of the shoulder, hand, and Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including ciprofloxacin. Post-marketing surveillance reports indicate that the risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

## **PRECAUTIONS**

**General:** INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local I.V. site reactions have been reported with the intravenous administration of

ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used. (See **ADVERSE REACTIONS**.)

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

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

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

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

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

Prescribing CIPRO IV in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

#### **Information For Patients:**

Patients should be advised:

- that antibacterial drugs including CIPRO IV should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When CIPRO IV is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by CIPRO IV or other antibacterial drugs in the future.
- that ciprofloxacin may be associated with hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
- that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should know how they react to this drug before they operate an automobile or machinery or engage in activities requiring mental alertness or coordination.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.
- that ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See **WARNINGS, PRECAUTIONS, Pediatric Use and ADVERSE REACTIONS**.)

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

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

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

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

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

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

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

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

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Animal studies have shown that the combination of very high doses of quinolones and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

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

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

- Salmonella/Microsome Test (Negative)

- E. coli* DNA Repair Assay (Negative)

- Mouse Lymphoma Cell Forward Mutation Assay (Positive)

- Chinese Hamster V<sub>79</sub> Cell HGPRT Test (Negative)

- Syrian Hamster Embryo Cell Transformation Assay (Negative)

- Saccharomyces cerevisiae* Point Mutation Assay (Negative)

- Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion Assay (Negative)

- Rat Hepatocyte DNA Repair Assay (Positive)

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

- Rat Hepatocyte DNA Repair Assay

- Micronucleus Test (Mice)

- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>).

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<sup>2</sup>), 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.<sup>3</sup>

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 (approximately 0.7-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>) revealed no evidence of impairment.

**Pregnancy: Teratogenic Effects. Pregnancy Category C:** There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.<sup>7</sup>

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.<sup>8</sup> In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group (background incidence of major malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).<sup>9</sup> There were 70 ciprofloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin and to fluoroquinolones overall were both within background incidence ranges. No specific patterns of congenital abnormalities were found. The study did not reveal any clear adverse reactions due to in utero exposure to ciprofloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to ciprofloxacin during pregnancy.<sup>7,8</sup> However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

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, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4- and 1.3-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>) no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. (See **WARNINGS**.)

**Nursing Mothers:** Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. 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.

**Pediatric Use:** Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL PHARMACOLOGY**.)

#### *Inhalational Anthrax (Post-Exposure)*

Ciprofloxacin is indicated in pediatric patients for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate. For information regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

#### *Complicated Urinary Tract Infection and Pyelonephritis*

Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli*. Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including those related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract

infection and pyelonephritis within six weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

#### *Cystic Fibrosis*

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

Musculoskeletal adverse events in patients with cystic fibrosis were reported in 22% of the patients in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group. Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the comparison group. Other adverse events were similar in nature and frequency between treatment arms. One of sixty-seven patients developed arthritis of the knee nine days after a ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed knee effusion without other abnormalities eight months after treatment. However, the relationship of this event to the patient's course of ciprofloxacin can not be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

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

### **ADVERSE REACTIONS**

**Adverse Reactions in Adult Patients:** During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. Most of the adverse events reported were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was discontinued because of an adverse event in 1.8% of intravenously treated patients.

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

In clinical trials the following events were reported, regardless of drug relationship, in greater than 1% of patients treated with intravenous ciprofloxacin : nausea, diarrhea, central nervous system disturbance, local I.V. site reactions, liver function tests abnormal eosinophilia, headache, restlessness, and rash. Many of these events were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment. Local I.V. site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

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

**BODY AS A WHOLE:** abdominal pain/discomfort, foot pain, pain, pain in extremities

**CARDIOVASCULAR:** cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine

**CENTRAL NERVOUS SYSTEM:** convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, abnormal gait, grand mal convulsion, anorexia

**GASTROINTESTINAL:** ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric pain, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, hepatitis, painful oral mucosa

**HEMIC/LYMPHATIC:** agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia

**METABOLIC/NUTRITIONAL:** amylase increase, lipase increase

**MUSCULOSKELETAL:** arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis

**RENAL/UROGENITAL:** renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.

**RESPIRATORY:** respiratory arrest, pulmonary embolism, dyspnea, laryngeal or pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccup, bronchospasm

**SKIN/HYPERSENSITIVITY:** allergic reactions, anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity (See **WARNINGS**.)

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

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

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

**Adverse Reactions in Pediatric Patients:** Ciprofloxacin, administered I.V. and /or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.

An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0 % (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms), usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received I.V. or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were



consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.

An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.

#### Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC

	Ciprofloxacin	Comparator
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6.0%)
95% Confidence Interval*	(-0.8%, +7.2%)	
Age Group		
≥ 12 months < 24 months	1/36 (2.8%)	0/41
≥ 2 years < 6 years	5/124 (4.0%)	3/118 (2.5%)
≥ 6 years < 12 years	18/143 (12.6%)	12/153 (7.8%)
≥ 12 years to 17 years	7/32 (21.9%)	6/37 (16.2 %)
All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, +9.1%)	

\*The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than + 6%. At both the 6 week and 1 year evaluations, the 95% confidence interval indicated that it could not be concluded that the ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.

In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse events were observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or post-marketing experience may also occur in pediatric patients.

**Post-Marketing Adverse Events:** The following adverse events have been reported from worldwide marketing experience with quinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.

Agitation, agranulocytosis, albuminuria, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure, hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, monoliasis (oral, gastrointestinal, vaginal) myalgia, myasthenia, myasthenia gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), phenytoin alteration (serum), potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.), psychosis (toxic), renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis. (See **PRECAUTIONS.**)

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

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

Other changes occurring infrequently were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of serum gamma-glutamyl transpeptidase ( $\gamma$  GT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol. Other changes occurring rarely during administration of ciprofloxacin were: elevation of serum amylase, decrease of blood glucose, pancytopenia, leukocytosis, elevated sedimentation rate, change in serum phenytoin, decreased prothrombin time, hemolytic anemia, and bleeding diathesis.

### **OVERDOSAGE**

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

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

### **DOSAGE AND ADMINISTRATION - ADULTS**

CIPRO I.V. should be administered to adults by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table. Slow infusion of a dilute solution into a larger vein will minimize patient discomfort and reduce the risk of venous irritation. (See **Preparation of CIPRO I.V. for Administration section.**)

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

### **ADULT DOSAGE GUIDELINES**

<b>Infection<sup>†</sup></b>	<b>Severity</b>	<b>Dose</b>	<b>Frequency</b>	<b>Usual Duration</b>
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10-14 Days

Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe			
	Ciprofloxacin + Piperacillin	400 mg	q8h	7-14 Days
		50 mg/kg Not to exceed 24 g/day	q4h	
Inhalational anthrax (post-exposure)**		400 mg	q12h	60 Days

\* 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, reasonably likely to predict clinical benefit.<sup>4</sup> For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**. Total duration of ciprofloxacin administration (I.V. or oral) for inhalational anthrax (post-exposure) is 60 days.

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

**Conversion of I.V. to Oral Dosing in Adults:** CIPRO Tablets and CIPRO Oral Suspension for oral administration are available. Parenteral therapy may be switched to oral CIPRO when the condition warrants, at the discretion of the physician. (See **CLINICAL PHARMACOLOGY** and table below for the equivalent dosing regimens.)

#### Equivalent AUC Dosing Regimens

CIPRO Oral Dosage	Equivalent CIPRO I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

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

**Adults with Impaired Renal Function:** Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment:

#### RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dosage
> 30	See usual dosage.
5 - 29	200-400 mg q 18-24 hr

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

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

Women:  $0.85 \times$  the value calculated for men.

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

For patients with changing renal function or for patients with renal impairment and hepatic insufficiency, careful monitoring is suggested.

## DOSAGE AND ADMINISTRATION - PEDIATRICS

CIPRO I.V. should be administered orally as described in the Dosage Guidelines table. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES**.)

Dosing and initial route of therapy (i.e., I.V. or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6 to 10 mg/kg I.V. every 8 hours and allowed to switch to oral therapy (10 to 20 mg/kg every 12 hours), at the discretion of the physician.

<b>PEDIATRIC DOSAGE GUIDELINES</b>				
Infection	Route of Administration	Dose (mg/kg)	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis  (patients from 1 to 17 years of age)	Intravenous	6 to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 8 hours	10-21 days*
	Oral	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing > 51 kg)	Every 12 hours	
Inhalational Anthrax (Post-Exposure)**	Intravenous	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
	Oral	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	

\* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).

\*\* Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.<sup>4</sup> For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (i.e., creatinine clearance of < 50 mL/min/1.73m<sup>2</sup>).

### **Preparation of CIPRO I.V. for Administration**

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

If the Y-type or “piggyback” method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the infusion of CIPRO I.V. If the concomitant use of CIPRO I.V. and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

**Flexible Containers:** CIPRO I.V. is also available as a 0.2% premixed solution in 5% dextrose in flexible containers of 100 mL or 200 mL. The solutions in flexible containers do not need to be diluted and may be infused as described above.

**COMPATIBILITY AND STABILITY**

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

- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP
- Sterile Water for Injection
- 10% Dextrose for Injection
- 5% Dextrose and 0.225% Sodium Chloride for Injection
- 5% Dextrose and 0.45% Sodium Chloride for Injection
- Lactated Ringer's for Injection

**HOW SUPPLIED**

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

**VIAL:** manufactured by Bayer Corporation and Hollister-Stier, Spokane, WA 99220.

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

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

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

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

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

**STORAGE**

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

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

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

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

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

\* Does not comply with USP with regards to “loss on drying” and “residue on ignition”.

**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 young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3- and 3.5-times the pediatric dose based upon comparative plasma AUCs) given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrototoxicity after an additional treatment-free period of 5 months. In another study, 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 was noted after single oral doses as low as 5 mg/kg (approximately 0.07-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>). 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 (approximately 0.2-times the highest recommended therapeutic dose based upon mg/m<sup>2</sup>).

In dogs, ciprofloxacin administered at 3 and 10 mg/kg by rapid intravenous injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release because they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid intravenous 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.

### INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

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

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD<sub>50</sub> (~5.5 x 10<sup>5</sup>) spores (range 5–30 LD<sub>50</sub>) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T<sub>max</sub> (1 hour post-dose) following oral dosing to steady-state ranged from 0.98 to 1.69 µg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL<sup>5</sup>. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p=0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.<sup>6</sup>

### CLINICAL STUDIES

#### EMPIRICAL THERAPY IN ADULT FEBRILE NEUTROPENIC PATIENTS

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

Clinical response rates observed in this study were as follows:

Outcomes	Ciprofloxacin/Piperacillin N = 233 Success (%)		Tobramycin/Piperacillin N = 237 Success (%)	
	Clinical Resolution of Initial Febrile Episode with No Modifications of Empirical Regimen*	63	(27.0%)	52

Clinical Resolution of Initial Febrile Episode Including Patients with Modifications of Empirical Regimen	187 (80.3%)	185 (78.1%)
Overall Survival	224 (96.1%)	223 (94.1%)

\* To be evaluated as a clinical resolution, patients had to have: (1) resolution of fever; (2) microbiological eradication of infection (if an infection was microbiologically documented); (3) resolution of signs/symptoms of infection; and (4) no modification of empirical antibiotic regimen.

### Complicated Urinary Tract Infection and Pyelonephritis – Efficacy in Pediatric Patients:

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.

Ciprofloxacin, administered I.V. and /or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) and pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety.

Patients were evaluated for clinical success and bacteriological eradication of the baseline organism(s) with no new infection or superinfection at 5 to 9 days post-therapy (Test of Cure or TOC). The Per Protocol population had a causative organism(s) with protocol specified colony count(s) at baseline, no protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).

The clinical success and bacteriologic eradication rates in the Per Protocol population were similar between ciprofloxacin and the comparator group as shown below.

#### Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	CIPRO	Comparator
Randomized Patients	337	352
Per Protocol Patients	211	231
Clinical Response at 5 to 9 Days Post-Treatment	95.7% (202/211)	92.6% (214/231)
95% CI [-1.3%, 7.3%]		
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
95% CI [-1.3%, 13.1%]		
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
<i>Escherichia coli</i>	156/178 (88%)	161/179 (90%)

\* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.

#### References:

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