

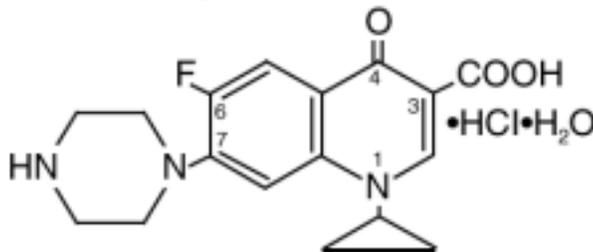
1 **CIPRO® (ciprofloxacin hydrochloride) TABLETS**
2 **CIPRO® (ciprofloxacin*) ORAL SUSPENSION**

3 **PZXXXXXX**

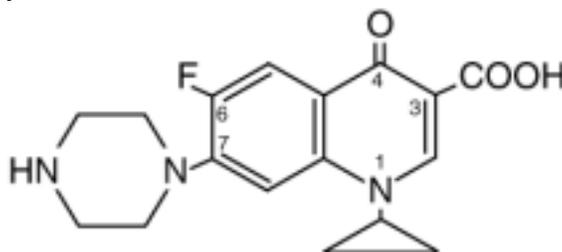
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4 **DESCRIPTION**

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



11 Ciprofloxacin is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic
12 acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its molecular weight is 331.4. It is a faintly
13 yellowish to light yellow crystalline substance and its chemical structure is as follows:
14



15 CIPRO film-coated tablets are available in 100 mg, 250 mg, 500 mg and 750 mg (ciprofloxacin
16 equivalent) strengths. Ciprofloxacin tablets are white to slightly yellowish. The inactive
17 ingredients are cornstarch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium
18 stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol and water.
19

20 Ciprofloxacin Oral Suspension is available in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g
21 ciprofloxacin in 100 mL) strengths. Ciprofloxacin Oral Suspension is a white to slightly yellowish
22 suspension with strawberry flavor which may contain yellow-orange droplets. It is composed of
23 ciprofloxacin microcapsules and diluent which are mixed prior to dispensing (See instructions
24 for USE/HANDLING). The components of the suspension have the following compositions:
25

26 Microcapsules - ciprofloxacin, polyvinylpyrrolidone, methacrylic acid copolymer, hydroxypropyl
27 methylcellulose, magnesium stearate, and Polysorbate 20.

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

29 * Does not comply with USP with regards to "loss on drying" and "residue on ignition".
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32

CLINICAL PHARMACOLOGY

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

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

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

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

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

Parameters	500 mg q12h, P.O.	400 mg q12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC (µg·hr/mL)	13.7 ^a	12.7 ^a	31.6 ^b	32.9 ^c
C_{max} (µg/mL)	2.97	4.56	3.59	4.07
^a AUC _{0-12h}	^b AUC _{24h} =AUC _{0-12h} x2		^c AUC _{24h} =AUC _{0-8h} x3	

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

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

81 CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of
82 the drug have been detected in the aqueous and vitreous humors of the eye.

83
84 **Metabolism:** Four metabolites have been identified in human urine which together account for
85 approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less
86 active than unchanged ciprofloxacin.

87
88 **Excretion:** The serum elimination half-life in subjects with normal renal function is
89 approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in
90 the urine as unchanged drug. After a 250-mg oral dose, urine concentrations of ciprofloxacin
91 usually exceed 200 µg/mL during the first two hours and are approximately 30 µg/mL at 8 to 12
92 hours after dosing. The urinary excretion of ciprofloxacin is virtually complete within 24 hours
93 after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute,
94 exceeds the normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion
95 would seem to play a significant role in its elimination. Co-administration of probenecid with
96 ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50%
97 increase in its concentration in the systemic circulation. Although bile concentrations of
98 ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small
99 amount of the dose administered is recovered from the bile as unchanged drug. An additional
100 1 to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20 to
101 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise
102 from either biliary clearance or transintestinal elimination.

103
104 With oral administration, a 500 mg dose, given as 10 mL of the 5% CIPRO Suspension
105 (containing 250 mg ciprofloxacin/5mL) is bioequivalent to the 500 mg tablet. A 10 mL volume of
106 the 5% CIPRO Suspension (containing 250 mg ciprofloxacin/5mL) is bioequivalent to a 5 mL
107 volume of the 10% CIPRO Suspension (containing 500 mg ciprofloxacin/5mL).

108
109 **Drug-drug Interactions:** When CIPRO Tablet is given concomitantly with food, there is a delay
110 in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after
111 dosing rather than 1 hour whereas there is no delay observed when CIPRO Suspension is
112 given with food. The overall absorption of CIPRO Tablet or CIPRO Suspension, however, is
113 not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are
114 also not affected by food. Concurrent administration of antacids containing magnesium
115 hydroxide or aluminum hydroxide may reduce the bioavailability of ciprofloxacin by as much as
116 90%. (See **PRECAUTIONS.**)

117
118 The serum concentrations of ciprofloxacin and metronidazole were not altered when these two
119 drugs were given concomitantly.

120
121 Concomitant administration of ciprofloxacin with theophylline decreases the clearance of
122 theophylline resulting in elevated serum theophylline levels and increased risk of a patient
123 development CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance
124 and inhibits the formation of paraxanthine after caffeine administration. (See **PRECAUTIONS.**)

125
126 **Special Populations:** Pharmacokinetic studies of the oral (single dose) and intravenous (single
127 and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin
128 are higher in elderly subjects (>65 years) as compared to young adults. Although the C_{max} is
129 increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least
130 partially attributed to decreased renal clearance in the elderly. Elimination half-life is only

131 slightly (~20%) prolonged in the elderly. These differences are not considered clinically
132 significant. (See **PRECAUTIONS: Geriatric Use.**)

133
134 In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged.
135 Dosage adjustments may be required. (See **DOSAGE AND ADMINISTRATION.**)

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

140
141 **Microbiology:** Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and
142 gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of
143 the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for
144 bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of
145 fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins,
146 aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these
147 classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known
148 cross-resistance between ciprofloxacin and other classes of antimicrobials. *In vitro* resistance
149 to ciprofloxacin develops slowly by multiple step mutations.

150
151 Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little effect
152 when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does not exceed
153 the minimal inhibitory concentration (MIC) by more than a factor of 2.

154
155 Ciprofloxacin has been shown to be active against most strains of the following
156 microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS AND**
157 **USAGE** section of the package insert for CIPRO (ciprofloxacin hydrochloride) Tablets and
158 CIPRO (ciprofloxacin) 5% and 10% Oral Suspension.

159
160 **Aerobic gram-positive microorganisms**

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

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

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

164 *Staphylococcus saprophyticus*

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

166 *Streptococcus pyogenes*

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Aerobic gram-negative microorganisms

<i>Campylobacter jejuni</i>	<i>Proteus mirabilis</i>
<i>Citrobacter diversus</i>	<i>Proteus vulgaris</i>
<i>Citrobacter freundii</i>	<i>Providencia rettgeri</i>
<i>Enterobacter cloacae</i>	<i>Providencia stuartii</i>
<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
<i>Haemophilus influenzae</i>	<i>Salmonella typhi</i>
<i>Haemophilus parainfluenzae</i>	<i>Serratia marcescens</i>
<i>Klebsiella pneumoniae</i>	<i>Shigella boydii</i>
<i>Moraxella catarrhalis</i>	<i>Shigella dysenteriae</i>
<i>Morganella morganii</i>	<i>Shigella flexneri</i>
<i>Neisseria gonorrhoeae</i>	<i>Shigella sonnei</i>

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 in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

<i>Staphylococcus haemolyticus</i>
<i>Staphylococcus hominis</i>
<i>Streptococcus pneumoniae</i> (penicillin-resistant strains only)

Aerobic gram-negative microorganisms

<i>Acinetobacter lwoffii</i>	<i>Pasteurella multocida</i>
<i>Aeromonas hydrophila</i>	<i>Salmonella enteritidis</i>
<i>Edwardsiella tarda</i>	<i>Vibrio cholerae</i>
<i>Enterobacter aerogenes</i>	<i>Vibrio parahaemolyticus</i>
<i>Klebsiella oxytoca</i>	<i>Vibrio vulnificus</i>
<i>Legionella pneumophila</i>	<i>Yersinia enterocolitica</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 method¹ (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:

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

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
221 ≤ 1	Susceptible (S)
222 2	Intermediate (I)
223 ≥ 4	Resistant (R)

224
225 ^aThese interpretive standards are applicable only to broth microdilution susceptibility tests with
226 streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

227
228 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
231 ≤ 1	Susceptible (S)

232
233 ^b This interpretive standard is applicable only to broth microdilution susceptibility tests with
234 *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium.¹

235
236 The current absence of data on resistant strains precludes defining any results other than
237 “Susceptible”. Strains yielding MIC results suggestive of a “nonsusceptible “ category should
238 be submitted to a reference laboratory for further testing.

239
240 For testing *Neisseria gonorrhoeae*^c:

<u>MIC (µg/mL)</u>	<u>Interpretation</u>
242 ≤ 0.06	Susceptible (S)
244 0.12 – 0.5	Intermediate (I)
245 ≥ 1	Resistant (R)

246
247 ^c This interpretive standard is applicable only to agar dilution test with GC agar base and 1%
248 defined growth supplement.

249
250 A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial
251 compound in the blood reaches the concentrations usually achievable. A report of
252 “Intermediate” indicates that the result should be considered equivocal, and, if the
253 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be
254 repeated. This category implies possible clinical applicability in body sites where the drug is
255 physiologically concentrated or in situations where high dosage of drug can be used. This
256 category also provides a buffer zone, which prevents small uncontrolled technical factors from
257 causing major discrepancies in interpretation. A report of “Resistant” indicates that the
258 pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the
259 concentrations usually achievable; other therapy should be selected.

260
 261 Standardized susceptibility test procedures require the use of laboratory control
 262 microorganisms to control the technical aspects of the laboratory procedures. Standard
 263 ciprofloxacin powder should provide the following MIC values:

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

273
 274 ^aThis quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth
 275 microdilution procedure using *Haemophilus* Test Medium (HTM).¹

276
 277 ^bThis quality control range is applicable to only *N. gonorrhoeae* ATCC 49226 tested by an agar
 278 dilution procedure using GC agar base and 1% defined growth supplement.

279
 280 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters also
 281 provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds.
 282 One such standardized procedure² requires the use
 283 of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-
 284 µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

285
 286 Reports from the laboratory providing results of the standard single-disk susceptibility test with
 287 a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:

288
 289 For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus*
 290 *parainfluenzae*, and *Neisseria gonorrhoeae*^a:

<u>Zone Diameter (mm)</u>	<u>Interpretation</u>
292 ≥21	Susceptible (S)
293 16-20	Intermediate (I)
294 ≤15	Resistant (R)

295
 296
 297 ^aThese zone diameter standards are applicable only to tests performed for streptococci using
 298 Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO₂.

299
 300 For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*^b:

<u>Zone Diameter(mm)</u>	<u>Interpretation</u>
302 ≥21	Susceptible (S)

303
 304
 305 ^bThis zone diameter standard is applicable only to tests with *Haemophilus influenzae* and
 306 *Haemophilus parainfluenzae* using *Haemophilus* Test Medium (HTM).²

307

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

311 For testing *Neisseria gonorrhoeae*^c:

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

318 ^cThis zone diameter standard is applicable only to disk diffusion tests with GC agar base and
319 1% defined growth supplement.

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

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

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

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

339 ^b These quality control limits are applicable only to tests conducted with *N. gonorrhoeae* ATCC
340 49226 performed by disk diffusion using GC agar base and 1% defined growth supplement.

342 INDICATIONS AND USAGE

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

348 **Urinary Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter*
349 *cloacae*, *Serratia marcescens*, *Proteus mirabilis*, *Providencia rettgeri*, *Morganella morganii*,
350 *Citrobacter diversus*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus*
351 *epidermidis*, *Staphylococcus saprophyticus*, or *Enterococcus faecalis*.

352
353 **Acute Uncomplicated Cystitis in females** caused by *Escherichia coli* or *Staphylococcus*
354 *saprophyticus*. (See **DOSAGE AND ADMINISTRATION**.)

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

357
358 **Lower Respiratory Tract Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*,
359 *Enterobacter cloacae*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*,
360 *Haemophilus parainfluenzae*, or *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the
361 treatment of acute exacerbations of chronic bronchitis.

362
363 NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the
364 treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae*.

365
366 **Acute Sinusitis** caused by *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Moraxella*
367 *catarrhalis*.

368
369 **Skin and Skin Structure Infections** caused by *Escherichia coli*, *Klebsiella pneumoniae*,
370 *Enterobacter cloacae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia stuartii*, *Morganella*
371 *morganii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* (methicillin-
372 susceptible), *Staphylococcus epidermidis*, or *Streptococcus pyogenes*.

373
374 **Bone and Joint Infections** caused by *Enterobacter cloacae*, *Serratia marcescens*, or
375 *Pseudomonas aeruginosa*.

376
377 **Complicated Intra-Abdominal Infections** (used in combination with metronidazole) caused by
378 *Escherichia coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Klebsiella pneumoniae*, or
379 *Bacteroides fragilis*. (See **DOSAGE AND ADMINISTRATION**.)

380
381 **Infectious Diarrhea** caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni*,
382 *Shigella boydii**, *Shigella dysenteriae*, *Shigella flexneri* or *Shigella sonnei** when antibacterial
383 therapy is indicated.

384
385 **Typhoid Fever (Enteric Fever)** caused by *Salmonella typhi*.

386
387 NOTE: The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has
388 not been demonstrated.

389
390 **Uncomplicated cervical and urethral gonorrhea** due to *Neisseria gonorrhoeae*.

391
392 **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of disease
393 following exposure to aerosolized *Bacillus anthracis*.

394
395 Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint
396 reasonably likely to predict clinical benefit and provide the basis for this indication.⁴ (See also,
397 **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**).

398
399 *Although treatment of infections due to this organism in this organ system demonstrated a
400 clinically significant outcome, efficacy was studied in fewer than 10 patients.

401
402 If anaerobic organisms are suspected of contributing to the infection, appropriate therapy
403 should be administered. Appropriate culture and susceptibility tests should be performed
404 before treatment in order to isolate and identify organisms causing infection and to determine
405 their susceptibility to ciprofloxacin. Therapy with CIPRO may be initiated before results of these

406 tests are known; once results become available appropriate therapy should be continued. As
407 with other drugs, some strains of *Pseudomonas aeruginosa* may develop resistance fairly
408 rapidly during treatment with ciprofloxacin. Culture and susceptibility testing performed
409 periodically during therapy will provide information not only on the therapeutic effect of the
410 antimicrobial agent but also on the possible emergence of bacterial resistance.

411 412 **CONTRAINDICATIONS**

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

415 416 **WARNINGS**

417 **THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND**
418 **ADOLESCENTS (LESS THAN 18 YEARS OF AGE), - EXCEPT FOR USE IN INHALATIONAL**
419 **ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE**
420 **NOT BEEN ESTABLISHED.** (See **PRECAUTIONS: Pediatric Use, Pregnancy, and Nursing**
421 **Mothers** subsections.) The oral administration of ciprofloxacin caused lameness in immature
422 dogs. Histopathological examination of the weight-bearing joints of these dogs revealed
423 permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of
424 cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various
425 species. (See **ANIMAL PHARMACOLOGY**.)

426
427 Convulsions, increased intracranial pressure, and toxic psychosis have been reported in
428 patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central
429 nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations,
430 depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first
431 dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be
432 discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should
433 be used with caution in patients with known or suspected CNS disorders that may predispose to
434 seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the
435 presence of other risk factors that may predispose to seizures or lower the seizure threshold
436 (e.g. certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General, Information for**
437 **Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

438
439 **SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING**
440 **CONCURRENT ADMINISTRATION OF CIPROFLOXACIN AND THEOPHYLLINE.** These
441 reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure.
442 Although similar serious adverse effects have been reported in patients receiving theophylline
443 alone, the possibility that these reactions may be potentiated by ciprofloxacin cannot be
444 eliminated. If concomitant use cannot be avoided, serum levels of theophylline should be
445 monitored and dosage adjustments made as appropriate.

446
447 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first
448 dose, have been reported in patients receiving quinolone therapy. Some reactions were
449 accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial
450 edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity
451 reactions. Serious anaphylactic reactions require immediate emergency treatment with
452 epinephrine. Oxygen, intravenous steroids, and airway management, including intubation,
453 should be administered as indicated.

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

460
461 **Pseudomembranous colitis has been reported with nearly all antibacterial agents,**
462 **including ciprofloxacin, and may range in severity from mild to life-threatening.**
463 **Therefore, it is important to consider this diagnosis in patients who present with**
464 **diarrhea subsequent to the administration of antibacterial agents.**

465
466 Treatment with antibacterial agents alters the normal flora of the colon and may permit
467 overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one
468 primary cause of “antibiotic-associated colitis.”

469
470 After the diagnosis of pseudomembranous colitis has been established, therapeutic measures
471 should be initiated. Mild cases of pseudomembranous colitis usually respond to drug
472 discontinuation alone. In moderate to severe cases, consideration should be given to
473 management with fluids and electrolytes, protein supplementation, and treatment with an
474 antibacterial drug clinically effective against *C. difficile* colitis.

475
476 Achilles and other tendon ruptures that required surgical repair or resulted in prolonged
477 disability have been reported with ciprofloxacin and other quinolones. Ciprofloxacin should be
478 discontinued if the patient experiences pain, inflammation, or rupture of a tendon.

479
480 Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial
481 agents used in high dose for short periods of time to treat gonorrhea may mask or delay the
482 symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for
483 syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up
484 serologic test for syphilis after three months.

485

486 PRECAUTIONS

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

493

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

497

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

500

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

505
506 As with any potent drug, periodic assessment of organ system functions, including renal,
507 hepatic, and hematopoietic function, is advisable during prolonged therapy.
508

509 **Information for Patients:**

510 Patients should be advised:

- 511 ◆ that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with
512 other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum
513 antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder,
514 or with other products containing calcium, iron or zinc should be avoided. Ciprofloxacin may
515 be taken two hours before or six hours after taking these products. Ciprofloxacin should not
516 be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since
517 absorption of ciprofloxacin may be significantly reduced; however, ciprofloxacin may be
518 taken with a meal that contains these products.
519
- 520 ◆ that ciprofloxacin may be associated with hypersensitivity reactions, even following a single
521 dose, and to discontinue the drug at the first sign of a skin rash or other allergic reaction.
522
- 523 ◆ to avoid excessive sunlight or artificial ultraviolet light while receiving ciprofloxacin and to
524 discontinue therapy if phototoxicity occurs.
525
- 526 ◆ to discontinue treatment; rest and refrain from exercise; and inform their physician if they
527 experience pain, inflammation, or rupture of a tendon.
528
- 529 ◆ that ciprofloxacin may cause dizziness and lightheadedness; therefore, patients should
530 know how they react to this drug before they operate an automobile or machinery or engage
531 in activities requiring mental alertness or coordination.
532
- 533 ◆ that ciprofloxacin may increase the effects of theophylline and caffeine. There is a
534 possibility of caffeine accumulation when products containing caffeine are consumed while
535 taking quinolones.
536
- 537 ◆ that convulsions have been reported in patients receiving quinolones, including
538 ciprofloxacin, and to notify their physician before taking this drug if there is a history of this
539 condition.

540
541 **Drug Interactions:** As with some other quinolones, concurrent administration of ciprofloxacin
542 with theophylline may lead to elevated serum concentrations of theophylline and prolongation of
543 its elimination half-life. This may result in increased risk of theophylline-related adverse
544 reactions. (See **WARNINGS**.) If concomitant use cannot be avoided, serum levels of
545 theophylline should be monitored and dosage adjustments made as appropriate.
546

547 Some quinolones, including ciprofloxacin, have also been shown to interfere with the
548 metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of
549 its serum half-life.
550

551 Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-
552 containing products such as magnesium/aluminum antacids, sucralfate, Videx® (didanosine)
553 chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc may
554 substantially decrease its absorption, resulting in serum and urine levels considerably lower

555 than desired. (See **DOSAGE AND ADMINISTRATION** for concurrent administration of these
556 agents with ciprofloxacin.)

557
558 Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability of
559 ciprofloxacin.

560
561 Altered serum levels of phenytoin (increased and decreased) have been reported in patients
562 receiving concomitant ciprofloxacin.

563
564 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare
565 occasions, resulted in severe hypoglycemia.

566
567 Some quinolones, including ciprofloxacin, have been associated with transient elevations in
568 serum creatinine in patients receiving cyclosporine concomitantly.

569
570 Quinolones have been reported to enhance the effects of the oral anticoagulant warfarin or its
571 derivatives. When these products are administered concomitantly, prothrombin time or other
572 suitable coagulation tests should be closely monitored.

573
574 Probenecid interferes with renal tubular secretion of ciprofloxacin and produces
575 an increase in the level of ciprofloxacin in the serum. This should be considered
576 if patients are receiving both drugs concomitantly.

577
578 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Eight *in vitro* mutagenicity tests have
579 been conducted with ciprofloxacin, and the test results are listed below:

- 580 Salmonella/Microsome Test (Negative)
- 581 *E. coli* DNA Repair Assay (Negative)
- 582 Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- 583 Chinese Hamster V₇₉ Cell HGPRT Test (Negative)
- 584 Syrian Hamster Embryo Cell Transformation Assay (Negative)
- 585 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
- 586 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion
- 587 Assay (Negative)
- 588 Rat Hepatocyte DNA Repair Assay (Positive)

590
591 Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test systems gave
592 negative results:

- 593 Rat Hepatocyte DNA Repair Assay
- 594 Micronucleus Test (Mice)
- 595 Dominant Lethal Test (Mice)

596
597
598 Long-term carcinogenicity studies in mice and rats have been completed. After daily oral doses
599 of 750 mg/kg (mice) and 250 mg/kg (rats) were administered for up to 2 years, there was no
600 evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

601
602 Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the
603 time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1)
604 mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks

605 while concurrently being administered ciprofloxacin. The time to development of the first skin
606 tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose
607 approximately equal to maximum recommended human dose based upon mg/m^2), as opposed
608 to 34 weeks when animals were treated with both UVA and vehicle. The times to development
609 of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other
610 quinolones.³

611
612 In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors.
613 There are no data from similar models using pigmented mice and/or fully haired mice. The
614 clinical significance of these findings to humans is unknown.

615
616 Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (0.8 times the
617 highest recommended human dose of 1200 mg based upon body surface area) revealed no
618 evidence of impairment.

619

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

621

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

627

628 A controlled prospective observational study followed 200 women exposed to fluoroquinolones-
629 (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation.⁸ In utero
630 exposure to fluoroquinolones during embryogenesis was not associated with increased risk of
631 major malformations. The reported rates of major congenital malformations were 2.2% for the
632 fluoroquinolone group and 2.6% for the control group (background incidence of major
633 malformations is 1-5%). Rates of spontaneous abortions, prematurity and low birth weight did
634 not differ between the groups and there were no clinically significant musculoskeletal
635 dysfunctions up to one year of age in the ciprofloxacin exposed children.

636

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

643

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

651

652 Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg
653 (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively)
654 and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits,

655 ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in
656 maternal weight loss and an increased incidence of abortion, but no teratogenicity was
657 observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal
658 toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. (See
659 **WARNINGS**.)
660

661 **Nursing Mothers:** Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin
662 absorbed by the nursing infant is unknown. Because of the potential for serious adverse
663 reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made
664 whether to discontinue nursing or to discontinue the drug, taking into account the importance of
665 the drug to the mother.
666

667 **Pediatric Use:** Safety and effectiveness in pediatric patients and adolescents less than 18
668 years of age have not been established, except for use in inhalational anthrax (post-exposure).
669 Ciprofloxacin causes arthropathy in juvenile animals. (See **WARNINGS**.)
670

671 For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates
672 that administration of ciprofloxacin to pediatric patients is appropriate. For information
673 regarding pediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND**
674 **ADMINISTRATION** and **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.
675

676 Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a
677 randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in
678 cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose
679 q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days
680 treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and
681 tobramycin I.V. 3 mg/kg/dose q8h for a total of 10 - 21 days. Patients less than 5 years of age
682 were not studied. Safety monitoring in the study included periodic range of motion examinations
683 and gait assessments by treatment-blinded examiners. Patients were followed for an average of
684 23 days after completing treatment (range 0-93 days). This study was not designed to
685 determine long term effects and the safety of repeated exposure to ciprofloxacin.
686

687 In the study, injection site reactions were more common in the ciprofloxacin group (24%) than in
688 the comparison group (8%). Other adverse events were similar in nature and frequency
689 between treatment arms. Musculoskeletal adverse events were reported in 22% of the patients
690 in the ciprofloxacin group and 21% in the comparison group. Decreased range of motion was
691 reported in 12% of the subjects in the ciprofloxacin group and 16% in the comparison group.
692 Arthralgia was reported in 10% of the patients in the ciprofloxacin group and 11% in the
693 comparison group. One of sixty-seven patients developed arthritis of the knee nine days after a
694 ten day course of treatment with ciprofloxacin. Clinical symptoms resolved, but an MRI showed
695 knee effusion without other abnormalities eight months after treatment. However, the
696 relationship of this event to the patient's course of ciprofloxacin can not be definitively
697 determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as
698 part of their underlying disease process.
699

700 **Geriatric Use :** In a retrospective analysis of 23 multiple-dose controlled clinical trials of
701 ciprofloxacin encompassing over 3500 ciprofloxacin treated patients, 25% of patients were
702 greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of
703 age. No overall differences in safety or effectiveness were observed between these subjects
704 and younger subjects, and other reported clinical experience has not identified differences in

705 responses between the elderly and younger patients, but greater sensitivity of some older
706 individuals on any drug therapy cannot be ruled out. Ciprofloxacin is known to be substantially
707 excreted by the kidney, and the risk of adverse reactions may be greater in patients with
708 impaired renal function. No alteration of dosage is necessary for patients greater than 65 years
709 of age with normal renal function. However, since some older individuals experience reduced
710 renal function by virtue of their advanced age, care should be taken in dose selection for elderly
711 patients, and renal function monitoring may be useful in these patients. (See **CLINICAL**
712 **PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**.)

713 714 **ADVERSE REACTIONS**

715 During clinical investigation with the tablet, 2,799 patients received 2,868 courses of the drug.
716 Most of the adverse events reported were described as only mild or moderate in severity,
717 abated soon after the drug was discontinued, and required no treatment. Ciprofloxacin was
718 discontinued because of an adverse event in 3.5% of patients treated.

719
720 The most frequently reported events, drug related or not, were nausea (5.2%), diarrhea (2.3%),
721 vomiting (2.0%), abdominal pain/discomfort (1.7%), headache (1.2%), restlessness (1.1%), and
722 rash (1.1%).

723
724 Additional events that occurred in less than 1% of ciprofloxacin patients are listed below.

725
726 **BODY AS A WHOLE:** foot pain

727 **CARDIOVASCULAR:** palpitation, atrial flutter, ventricular ectopy, syncope, hypertension,
728 angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis

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

733 **PRECAUTIONS**.)

734 **GASTROINTESTINAL:** painful oral mucosa, oral candidiasis, dysphagia,
735 intestinal perforation, gastrointestinal bleeding (See above.) Cholestatic
736 jaundice has been reported.

737 **HEMIC/LYMPHATIC:** lymphadenopathy

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

740 **RENAL/UROGENITAL:** interstitial nephritis, nephritis, renal failure, polyuria,
741 urinary retention, urethral bleeding, vaginitis, acidosis, breast pain

742 **RESPIRATORY:** dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough,
743 hemoptysis, bronchospasm, pulmonary embolism

744 **SKIN/HYPERSENSITIVITY:** pruritus, urticaria, photosensitivity, flushing, fever,
745 chills, angioedema, edema of the face, neck, lips, conjunctivae or hands,
746 cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.)

747 Allergic reactions ranging from urticaria to anaphylactic reactions have been
748 reported. (See **WARNINGS**.)

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

752

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

756
757 In randomized, double-blind controlled clinical trials comparing ciprofloxacin tablets (500 mg
758 BID) to cefuroxime axetil (250 mg - 500 mg BID) and to clarithromycin (500 mg BID) in patients
759 with respiratory tract infections, ciprofloxacin demonstrated a CNS adverse event profile
760 comparable to the control drugs.

761
762 **Post-Marketing Adverse Events:** Additional adverse events, regardless of relationship to
763 drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin,
764 are:

765
766 agitation, agranulocytosis, albuminuria, anaphylactic reactions, anosmia, candiduria, cholesterol
767 elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema
768 multiforme, exfoliative dermatitis, flatulence, glucose elevation (blood), hemolytic anemia,
769 hepatic necrosis, hypotension (postural), jaundice, methemoglobinemia, myalgia, myasthenia
770 gravis (possible exacerbation), myoclonus, nystagmus, pancreatitis, phenytoin alteration
771 (serum), potassium elevation (serum), prothrombin time prolongation, pseudomembranous
772 colitis (The onset of pseudomembranous colitis symptoms may occur during or after
773 antimicrobial treatment.), psychosis (toxic), renal calculi, Stevens-Johnson syndrome, taste
774 loss, tendinitis, tendon rupture, toxic epidermal necrolysis, triglyceride elevation (serum),
775 vaginal candidiasis, and vasculitis (See **PRECAUTIONS.**)

776
777 **Adverse Laboratory Changes:** Changes in laboratory parameters listed as adverse events
778 without regard to drug relationship are listed below:

779
780 Hepatic - Elevations of ALT (SGPT) (1.9%), AST (SGOT) (1.7%),
781 alkaline phosphatase (0.8%), LDH (0.4%), serum bilirubin (0.3%).
782 Hematologic - Eosinophilia (0.6%), leukopenia (0.4%), decreased blood
783 platelets (0.1%), elevated blood platelets (0.1%),
784 pancytopenia (0.1%).
785 Renal -Elevations of serum creatinine (1.1%), BUN (0.9%),
786 CRYSTALLURIA, CYLINDRURIA, AND HEMATURIA HAVE
787 BEEN REPORTED.

788
789 Other changes occurring in less than 0.1% of courses were: elevation of serum gammaglutamyl
790 transferase, elevation of serum amylase, reduction in blood glucose, elevated uric acid,
791 decrease in hemoglobin, anemia, bleeding diathesis, increase in blood monocytes,
792 leukocytosis.

793 794 **OVERDOSAGE**

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

799
800 Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in
801 mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period at
802 the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500 mg/kg in

803 the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent species and
804 severe vomiting in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin >
805 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after dosing.

806
807 In mice, rats, rabbits and dogs, significant toxicity including tonic/clonic convulsions was
808 observed at intravenous doses of ciprofloxacin between 125 and 300 mg/kg.

809

810 **DOSAGE AND ADMINISTRATION**

811 CIPRO Tablets and Oral Suspension should be administered orally as described in the Dosage
812 Guidelines table.

813

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

817

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

DOSAGE GUIDELINES				
Infection	Type or Severity	Unit Dose	Frequency	Usual Durations[†]
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)**	Adult	500 mg	q 12 h	60 Days
	Pediatric	15 mg/kg per dose, not to exceed 500 mg per dose	q 12 h	60 Days

824 * used in conjunction with metronidazole

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

827 ** Drug administration should begin as soon as possible after suspected or confirmed exposure.

828 This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans,
829 reasonably likely to predict clinical benefit.⁴ For a discussion of ciprofloxacin serum concentrations in
830 various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION**.

831
832 Patients whose therapy is started with CIPRO I.V. may be switched to CIPRO Tablets or Oral
833 Suspension when clinically indicated at the discretion of the physician (See **CLINICAL**
834 **PHARMACOLOGY** and table below for the equivalent dosing regimens).

835

836 **Equivalent AUC Dosing Regimens**

Cipro Oral Dosage

250 mg Tablet q 12 h

500 mg Tablet q 12 h

750 mg Tablet q 12 h

Equivalent Cipro I.V Dosage

200 mg I.V. q 12 h

400 mg I.V. q 12 h

400 mg I.V. q 8 h

837

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

843 table provides dosage guidelines for use in patients with renal impairment; however, monitoring
844 of serum drug levels provides the most reliable basis for dosage adjustment:

845
846 **RECOMMENDED STARTING AND MAINTENANCE DOSES**
847 **FOR PATIENTS WITH IMPAIRED RENAL FUNCTION**

848

849 Creatinine Clearance (mL/min)	849 Dose
850 >50	850 See Usual Dosage.
851 30 - 50	851 250-500 mg q 12 h
852 5 - 29	852 250-500 mg q 18 h
853 Patients on hemodialysis 854 or Peritoneal dialysis)	853 250-500 mg q 24 h (after dialysis)

855

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

858

$$859 \text{ Men: Creatinine clearance (mL/min) = } \frac{\text{Weight (kg) x (140-age)}}{72 \times \text{serum creatinine (mg/dL)}}$$

860

861 Women: 0.85 x the value calculated for men.

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

863
864 In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be
865 administered at the intervals noted above; however, patients should be carefully monitored and
866 the serum ciprofloxacin concentration should be measured periodically. Peak concentrations
867 (1-2 hours after dosing) should generally range from 2 to 4 µg/mL.

868
869 For patients with changing renal function or for patients with renal impairment and hepatic
870 insufficiency, measurement of serum concentrations of ciprofloxacin will provide additional
871 guidance for adjusting dosage.

872
873
874 **HOW SUPPLIED**

875
876 CIPRO (ciprofloxacin hydrochloride) Tablets are available as round, slightly yellowish film-
877 coated tablets containing 100 mg or 250 mg ciprofloxacin. The 100 mg tablet is coded with the
878 word "CIPRO" on one side and "100" on the reverse side. The 250 mg tablet is coded with the
879 word "CIPRO" on one side and "250" on the reverse side. CIPRO is also available as capsule
880 shaped, slightly yellowish film-coated tablets containing 500-mg or 750 mg ciprofloxacin. The
881 500 mg tablet is coded with the word "CIPRO" on one side and "500" on the reverse side. The
882 750 mg tablet is coded with the word "CIPRO" on one side and "750" on the reverse side.
883 CIPRO 250 mg, 500 mg, and 750 mg are available in bottles of 50, 100, and Unit Dose
884 packages of 100. The 100 mg strength is available only as CIPRO Cystitis pack containing 6
885 tablets for use only in female patients with acute uncomplicated cystitis.

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	Strength	NDC Code	Tablet Identification
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
Unit Dose			
Package of 100:	250 mg	NDC 0026-8512-48	CIPRO 250
	500 mg	NDC 0026-8513-48	CIPRO 500
	750 mg	NDC 0026-8514-48	CIPRO 750
Cystitis			
Package of 6:	100 mg	NDC 0026-8511-06	CIPRO 100

Store below 30°C (86°F).

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

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

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

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

ANIMAL PHARMACOLOGY

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

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

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

934
935 In mice, concomitant administration of nonsteroidal anti-inflammatory drugs such as
936 phenylbutazone and indomethacin with quinolones has been reported to enhance the CNS
937 stimulatory effect of quinolones.

938
939 Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated
940 animals.

941

942

CLINICAL STUDIES

943 **Uncomplicated Cystitis**

944 Two double-blind, controlled clinical studies of acute uncomplicated cystitis in women were
945 performed in the U.S. At the 5-9 day post-therapy follow-up visit, the clinical resolution rates in
946 the first study, which compared ciprofloxacin 100 mg BID for 3 days to ciprofloxacin 250 mg
947 BID for 7 days, were 87% (82/94) and 94%, (81/86), respectively. For *E. coli*, the bacteriological
948 eradication rates for the first study were 91% (64/70) in the ciprofloxacin 100 mg regimen and
949 97% (67/69) in the ciprofloxacin 250 mg regimen. The second study's bacteriological
950 eradication rates were 95% (117/123) for the ciprofloxacin 100 mg regimen and 98% (103/105)
951 for the control regimen. Pooled eradication rates for the ciprofloxacin 100 mg treatment arms
952 were 100% (16/16) for *S. saprophyticus*.

953

954

INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

955 The mean serum concentrations of ciprofloxacin associated with a statistically significant
956 improvement in survival in the rhesus monkey model of inhalational anthrax are reached or
957 exceeded in adult and pediatric patients receiving oral and intravenous regimens. (See
958 **DOSAGE AND ADMINISTRATION**.) Ciprofloxacin pharmacokinetics have been evaluated in
959 various human populations. The mean peak serum concentration achieved at steady state in
960 human adults receiving 500 mg orally every 12 hours is 2.97 µg/ml, and 4.56 µg/ml following
961 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for
962 both of these regimens is 0.2 µg/ml. In a study of 10 pediatric patients between 6 and 16 years
963 of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations
964 range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg
965 administered 12 hours apart. After the second intravenous infusion patients switched to 15
966 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial
967 oral dose. Long-term safety data, including effects on cartilage, following the administration of
968 ciprofloxacin to pediatric patients are limited. (For additional information, see **PRECAUTIONS**,
969 **Pediatric Use**.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate
970 endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.⁴

971

972 A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11
973 LD₅₀ (~5.5 x 10⁵ spores (range 5-30 LD₅₀) of *B. anthracis* was conducted. The minimal
974 inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08
975 µg/ml. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected
976 T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/ml.
977 Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19
978 µg/ml⁵. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin

979 beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group
980 (9/10) [p= 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the
981 30-day drug administration period.⁶

982
983 **Instructions To The Pharmacist For Use/Handling Of CIPRO Oral Suspension:**

984
985 CIPRO Oral Suspension is supplied in 5% (5g ciprofloxacin in 100 mL) and 10% (10g
986 ciprofloxacin in 100 mL) strengths. The drug product is composed of two components
987 (microcapsules and diluent) which must be combined prior to dispensing.

988
989 One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250 mg of ciprofloxacin.
990 One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500 mg of ciprofloxacin.

991
992 **Appropriate Dosing Volumes of the Oral Suspensions:**

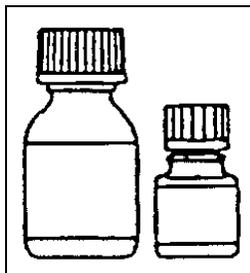
993

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

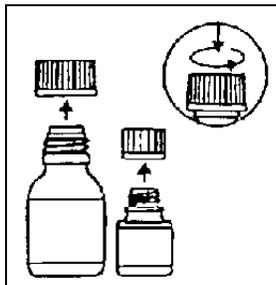
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999 **Preparation of the suspension:**

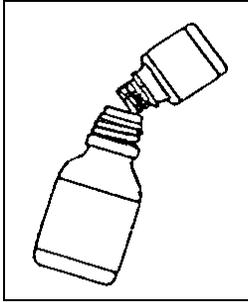
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1001 1. The small bottle contains the microcapsules, the large bottle contains
1002 the diluent.



1003
1004 2. Open both bottles. Child-proof cap: Press down according to
1005 instructions on the cap while turning to the left.

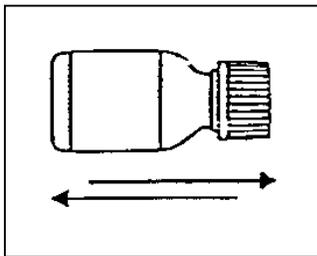


1006
1007 3. Pour the microcapsules completely into the larger bottle of diluent. **Do**
1008 **not add water to the suspension.**



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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.



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

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

References:

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1048 **PATIENT INFORMATION ABOUT**

1049 **CIPRO® (ciprofloxacin hydrochloride) TABLETS**

1050 **CIPRO® (ciprofloxacin) ORAL SUSPENSION**

1051
1052
1053 This section contains important patient information about CIPRO (ciprofloxacin hydrochloride)
1054 Tablets and CIPRO (ciprofloxacin) Oral Suspension and should be read completely before you
1055 begin treatment. This section does not take the place of discussion with your doctor or health
1056 care professional about your medical condition or your treatment. This section does not list all
1057 benefits and risks of CIPRO. If you have any concerns about you condition or your medicine,
1058 ask your doctor. Only your doctor can determine if CIPRO is right for you.
1059

1060 **What is CIPRO?**

1061
1062 CIPRO is an antibiotic used to treat bladder, kidney, prostate, cervix, stomach, intestine, lung,
1063 sinus, bone, and skin infections caused by certain germs called bacteria. CIPRO kills many
1064 types of bacteria that can infect these areas of the body. CIPRO has been shown in a large
1065 number of clinical trials to be safe and effective for the treatment of bacterial infections.
1066

1067 Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the
1068 common cold). CIPRO, like all other antibiotics, does not kill viruses. You should contact your
1069 doctor if your condition is not improving while taking CIPRO.
1070

1071 CIPRO Tablets are white to slightly yellow in color and are available in 100 mg, 250 mg, 500
1072 mg and 750 mg strengths. CIPRO Oral Suspension is white to slightly yellow in color and is
1073 available in concentrations of 250 mg per teaspoon (5%) and 500 mg per teaspoon (10%).
1074

1075 **How and when should I take CIPRO?**

1076 **CIPRO Tablets:**

1077
1078 Unless directed otherwise by your physician, CIPRO should be taken twice a day at
1079 approximately the same time, in the morning and in the evening. CIPRO can be taken with food
1080 or on an empty stomach. CIPRO should not be taken with dairy products (like milk or yogurt) or
1081 calcium-fortified juices alone; however, CIPRO may be taken with a meal that contains these
1082 products.
1083
1084

1085 You should take CIPRO for as long as your doctor prescribes it, even after you start to feel
1086 better. Stopping an antibiotic too early may result in failure to cure your infection. Do not take
1087 a double dose of CIPRO even if you miss a dose by mistake.

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CIPRO Oral Suspension:

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

Who should not take CIPRO?

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

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

In general, CIPRO is not recommended for persons less than 18 years of age.

What are the possible side effects of CIPRO?

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

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

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

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

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

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

1137 **What about other medications I am taking?**

1138

1139 CIPRO can affect how other medicines work. Tell your doctor about all other prescription and
1140 non-prescription medicines or supplements you are taking. This is especially important if you
1141 are taking theophylline. Other medications including warfarin, glyburide, and phenytoin may
1142 also interact with CIPRO.

1143

1144 Many antacids, multivitamins, and other dietary supplements containing magnesium, calcium,
1145 aluminum, iron or zinc can interfere with the absorption of CIPRO and may prevent it from
1146 working. Other medications such as sulcrafate and Videx® (didanosine) chewable/buffered
1147 tablets or pediatric powder may also stop CIPRO from working. You should take CIPRO either
1148 2 hours before or 6 hours after taking these products.

1149

1150 **What if I have been prescribed CIPRO for possible anthrax exposure?**

1151

1152 CIPRO has been approved to reduce the chance of developing anthrax infection following
1153 exposure to the anthrax bacteria. In general, CIPRO is not recommended for children;
1154 however, it is approved for use in patients younger than 18 years old for anthrax exposure. If
1155 you are pregnant, or plan to become pregnant while taking CIPRO, you and your doctor should
1156 discuss if the benefits of taking CIPRO for anthrax outweigh the risks.

1157

1158 CIPRO is generally well tolerated. Side effects that may occur during treatment to prevent
1159 anthrax might be acceptable due to the seriousness of the disease. You and your doctor
1160 should discuss the risks of not taking your medicine against the risks of experiencing side
1161 effects.

1162

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

1166

1167 Your doctor has prescribed CIPRO only for you. Do not give it to other people. Do not use it
1168 for a condition for which it was not prescribed. You should take your CIPRO for as long as your
1169 doctor prescribes it; stopping CIPRO too early may result in failure to prevent anthrax.

1170 **Remember:**

1171

1172 Do not give CIPRO to anyone other than the person for whom it was prescribed.

1173

1174 Take your dose of CIPRO in the morning and in the evening.

1175

1176 Complete the course of CIPRO even if you are feeling better.

1177

1178 Keep CIPRO and all medications out of reach of children.

1179

1180 **Bayer Corporation**

1181 **Pharmaceutical Division**

1182 **400 Morgan Lane**

1183 **West Haven, CT 06516 USA**

1184

1185 **Rx Only**

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1188
1189 CIPRO (ciprofloxacin*) 5% and 10% Oral Suspension Made in Italy. Printed in U.S.A.
1190
1191 * Does not comply with USP with regards to “loss on drying” and “residue on ignition”.

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/s/

Renata Albrecht
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