

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-554

Approved Labeling

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

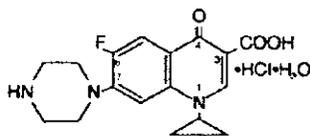
CIPRO® XR
(ciprofloxacin* extended-release tablets)

4 Revised Proposed PI

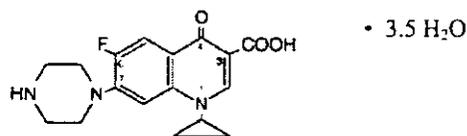
08/29/03

6 **DESCRIPTION**

7 CIPRO® XR (ciprofloxacin* extended-release tablets) contains ciprofloxacin, a synthetic
8 broad-spectrum antimicrobial agent for oral administration. CIPRO XR Tablets are coated,
9 bilayer tablets consisting of an immediate-release layer and an erosion-matrix type
10 controlled-release layer. The tablets contain a combination of two types of ciprofloxacin
11 drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin
12 hydrochloride is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-
13 quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the monohydrate and
14 the sesquihydrate. The empirical formula of the monohydrate is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$
15 and its molecular weight is 385.8. The empirical formula of the sesquihydrate is $C_{17}H_{18}FN_3O_3$
16 $\cdot HCl \cdot 1.5 H_2O$ and its molecular weight is 394.8. The drug substance is a faintly yellowish
17 to light yellow crystalline substance. The chemical structure of the monohydrate is as
18 follows:



20
21
22 Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-
23 quinolinecarboxylic acid. As a hydrate, its empirical formula is $C_{17}H_{18}FN_3O_3 \cdot 3.5 H_2O$ and
24 its molecular weight is 394.3. It is a pale yellowish to light yellow crystalline substance and
25 its chemical structure is as follows:



26
27
28
29 CIPRO XR is available in 500 mg and 1000 mg (ciprofloxacin equivalent) tablet strengths.
30 CIPRO XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets.
31 Each CIPRO XR 500 mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5
32 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin† (212.6 mg, calculated
33 on the dried basis). Each CIPRO XR 1000 mg tablet contains 1000 mg of ciprofloxacin as
34 ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on the dried basis) and
35 ciprofloxacin† (425.2 mg, calculated on the dried basis). The inactive ingredients are
36 croscopovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal
37 anhydrous, succinic acid, and titanium dioxide.

38

39 * as ciprofloxacin[†] and ciprofloxacin hydrochloride
40 [†] does not comply with the loss on drying test and residue on ignition test of the
41 USP monograph.
42

43 CLINICAL PHARMACOLOGY

44 Absorption

45 CIPRO XR Tablets are formulated to release drug at a slower rate compared to immediate-
46 release tablets. Approximately 35% of the dose is contained within an immediate-release
47 component, while the remaining 65% is contained in a slow-release matrix.
48

49
50 Maximum plasma ciprofloxacin concentrations are attained between 1 and 4 hours after
51 dosing with CIPRO XR. In comparison to the 250 mg and 500 mg ciprofloxacin immediate-
52 release BID treatment, the C_{max} of CIPRO XR 500 mg and 1000 mg once daily are higher
53 than the corresponding BID doses, while the AUCs over 24 hours are equivalent.
54

55 The following table compares the pharmacokinetic parameters obtained at steady state for
56 these four treatment regimens (500 mg QD CIPRO XR versus 250 mg BID ciprofloxacin
57 immediate-release tablets and 1000 mg QD CIPRO XR versus 500 mg BID ciprofloxacin
58 immediate-release).

59 Ciprofloxacin Pharmacokinetics (Mean ± SD) Following CIPRO® and CIPRO XR 60 Administration 61 62

	C _{max} (mg/L)	AUC _{0-24h} (mg•h/L)	T _{1/2} (hr)	T _{max} (hr) [§]
CIPRO XR 500 mg QD	1.59 ± 0.43	7.97 ± 1.87	6.6 ± 1.4	1.5 (1.0 – 2.5)
CIPRO 250 mg BID	1.14 ± 0.23	8.25 ± 2.15	4.8 ± 0.6	1.0 (0.5 – 2.5)
CIPRO XR 1000 mg QD	3.11 ± 1.08	16.83 ± 5.65	6.31 ± 0.72	2.0 (1 – 4)
CIPRO 500 mg BID	2.06 ± 0.41	17.04 ± 4.79	5.66 ± 0.89	2.0 (0.5 – 3.5)

63
64 § median (range)
65

66 Results of the pharmacokinetic studies demonstrate that CIPRO XR may be administered
67 with or without food (e.g. high-fat and low-fat meals or under fasted conditions).
68

69 Distribution

70 The volume of distribution calculated for intravenous ciprofloxacin is approximately 2.1 –
71 2.7 L/kg. Studies with the oral and intravenous forms of ciprofloxacin have demonstrated
72 penetration of ciprofloxacin into a variety of tissues. The binding of ciprofloxacin to serum
73 proteins is 20% to 40%, which is not likely to be high enough to cause significant protein
74 binding interactions with other drugs. Following administration of a single dose of CIPRO
75 XR, ciprofloxacin concentrations in urine collected up to 4 hours after dosing averaged over
76 300 mg/L for both the 500 mg and 1000 mg tablets; in urine excreted from 12 to 24 hours

77 after dosing, ciprofloxacin concentration averaged 27 mg/L for the 500 mg tablet, and 58
78 mg/L for the 1000 mg tablet.

79

80 **Metabolism**

81 Four metabolites of ciprofloxacin were identified in human urine. The metabolites have
82 antimicrobial activity, but are less active than unchanged ciprofloxacin. The primary
83 metabolites are oxociprofloxacin (M3) and sulfociprofloxacin (M2), each accounting for
84 roughly 3% to 8% of the total dose. Other minor metabolites are desethylene ciprofloxacin
85 (M1), and formylciprofloxacin (M4). The relative proportion of drug and metabolite in
86 serum corresponds to the composition found in urine. Excretion of these metabolites was
87 essentially complete by 24 hours after dosing.

88

89 **Elimination**

90 The elimination kinetics of ciprofloxacin are similar for the immediate-release and the
91 CIPRO XR tablet. In studies comparing the CIPRO XR and immediate-release ciprofloxacin,
92 approximately 35% of an orally administered dose was excreted in the urine as unchanged
93 drug for both formulations. The urinary excretion of ciprofloxacin is virtually complete
94 within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately
95 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL/minute. Thus,
96 active tubular secretion would seem to play a significant role in its elimination. Co-
97 administration of probenecid with immediate-release ciprofloxacin results in about a 50%
98 reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the
99 systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher
100 than serum concentrations after oral dosing with the immediate-release tablet, only a small
101 amount of the dose administered is recovered from the bile as unchanged drug. An additional
102 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately
103 20% to 35% of an oral dose of immediate-release ciprofloxacin is recovered from the feces
104 within 5 days after dosing. This may arise from either biliary clearance or transintestinal
105 elimination.

106

107 **Special Populations**

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

115

116 In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged.
117 No dose adjustment is required for patients with uncomplicated urinary tract infections
118 receiving 500 mg CIPRO XR. For complicated urinary tract infection and acute
119 uncomplicated pyelonephritis, where 1000 mg is the appropriate dose, the dosage of CIPRO
120 XR should be reduced to CIPRO XR 500 mg q 24 h in patients with creatinine clearance
121 below 30 mL/min. (See **DOSAGE AND ADMINISTRATION.**)

122

123 In studies in patients with stable chronic cirrhosis, no significant changes in ciprofloxacin
124 pharmacokinetics have been observed. The kinetics of ciprofloxacin in patients with acute
125 hepatic insufficiency, however, have not been fully elucidated. (See **DOSAGE AND**
126 **ADMINISTRATION.**)

127

128 **Drug-drug Interactions**

129 Previous studies with immediate-release ciprofloxacin have shown that concomitant
130 administration of ciprofloxacin with theophylline decreases the clearance of theophylline
131 resulting in elevated serum theophylline levels and increased risk of a patient developing
132 CNS or other adverse reactions. Ciprofloxacin also decreases caffeine clearance and inhibits
133 the formation of paraxanthine after caffeine administration. Absorption of ciprofloxacin is
134 significantly reduced by concomitant administration of multivalent cation-containing
135 products such as magnesium/aluminum antacids, sucralfate, VIDEX® (didanosine)
136 chewable/buffered tablets or pediatric powder, or products containing calcium, iron, or zinc.
137 (See **PRECAUTIONS, Drug Interactions and Information for Patients, and**
138 **DOSAGE AND ADMINISTRATION.**)

139

140 **Antacids:** When CIPRO XR given as a single 1000 mg dose (twice the recommended daily
141 dose) was administered two hours before, or four hours after a magnesium/aluminum-
142 containing antacid (900 mg aluminum hydroxide and 600 mg magnesium hydroxide as a
143 single oral dose) to 18 healthy volunteers, there was a 4% and 19% reduction, respectively, in
144 the mean C_{max} of ciprofloxacin. The reduction in the mean AUC was 24% and 26%,
145 respectively. CIPRO XR should be administered at least 2 hours before or 6 hours after
146 antacids containing magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine)
147 chewable/buffered tablets or pediatric powder, metal cations such as iron, and multivitamin
148 preparations with zinc. Although CIPRO XR may be taken with meals that include milk,
149 concomitant administration with dairy products or with calcium-fortified juices alone should
150 be avoided, since decreased absorption is possible. (See **PRECAUTIONS, Information**
151 **for Patients and Drug Interactions, and DOSAGE AND ADMINISTRATION.**)

152

153 **Omeprazole:** When CIPRO XR was administered as a single 1000 mg dose concomitantly
154 with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC
155 and C_{max} of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical
156 significance of this interaction has not been determined. (See **PRECAUTIONS, Drug**
157 **Interactions.**)

158

159 **MICROBIOLOGY**

160

161 Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive
162 organisms. The bactericidal action of ciprofloxacin results from inhibition of topoisomerase
163 II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), which are required for
164 bacterial DNA replication, transcription, repair, and recombination. The mechanism of action
165 of quinolones, including ciprofloxacin, is different from that of other antimicrobial agents

166 such as beta-lactams, macrolides, tetracyclines, or aminoglycosides; therefore, organisms
167 resistant to these drugs may be susceptible to ciprofloxacin. There is no known cross-
168 resistance between ciprofloxacin and other classes of antimicrobials. Resistance to
169 ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Resistance to ciprofloxacin
170 due to spontaneous mutations occurs at a general frequency of between $< 10^{-9}$ to 1×10^{-6} .

171
172 Ciprofloxacin is slightly less active when tested at acidic pH. The inoculum size has little
173 effect when tested *in vitro*. The minimal bactericidal concentration (MBC) generally does
174 not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

175
176 Ciprofloxacin has been shown to be active against most strains of the following
177 microorganisms, both *in vitro* and in clinical infections as described in the **INDICATIONS**
178 **AND USAGE** section.

179
Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately
susceptible.)

Staphylococcus saprophyticus

180

Aerobic gram-negative microorganisms

Escherichia coli

Klebsiella pneumoniae

Proteus mirabilis

Pseudomonas aeruginosa

181

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

183

184 Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 $\mu\text{g/mL}$ or less
185 against most ($\geq 90\%$) strains of the following microorganisms; however, the safety and
186 effectiveness of CIPRO XR in treating clinical infections due to these microorganisms have
187 not been established in adequate and well-controlled clinical trials.

188

189

Aerobic gram-negative microorganisms

Citrobacter koseri

Morganella morganii

Citrobacter freundii

Proteus vulgaris

Edwardsiella tarda

Providencia rettgeri

Enterobacter aerogenes

Providencia stuartii

Enterobacter cloacae

Serratia marcescens

Klebsiella oxytoca

190

Susceptibility Tests

191 **Dilution Techniques:** Quantitative methods are used to determine antimicrobial minimal
192 inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of
193 bacteria to antimicrobial compounds. The MICs should be determined using a standardized
194

195 procedure. Standardized procedures are based on a dilution method¹ (broth or agar) or
196 equivalent with standardized inoculum concentrations and standardized concentrations of
197 ciprofloxacin. The MIC values should be interpreted according to the following criteria:
198

199 For testing *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and
200 *Staphylococcus* species:
201

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

202
203 A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the
204 antimicrobial compound in the blood reaches the concentrations usually achievable. A report
205 of "Intermediate" indicates that the result should be considered equivocal, and, if the
206 microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should
207 be repeated. This category implies possible clinical applicability in body sites where the drug
208 is physiologically concentrated or in situations where high dosage of drug can be used. This
209 category also provides a buffer zone which prevents small uncontrolled technical factors from
210 causing major discrepancies in interpretation. A report of "Resistant" indicates that the
211 pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the
212 concentrations usually achievable; other therapy should be selected.
213

214 Standardized susceptibility test procedures require the use of laboratory control
215 microorganisms to control the technical aspects of the laboratory procedures. Standard
216 ciprofloxacin powder should provide the following MIC values:
217

<u>Microorganism</u>		<u>MIC Range (µg/mL)</u>
<i>Enterococcus faecalis</i>	ATCC 29212	0.25 – 2.0
<i>Escherichia coli</i>	ATCC 25922	0.004 – 0.015
<i>Staphylococcus aureus</i>	ATCC 29213	0.12 – 0.5
<i>Pseudomonas aeruginosa</i>	ATCC 27853	0.25 - 1

218
219 **Diffusion Techniques:** Quantitative methods that require measurement of zone diameters
220 also provide reproducible estimates of the susceptibility of bacteria to antimicrobial
221 compounds. One such standardized procedure² requires the use of standardized inoculum
222 concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test
223 the susceptibility of microorganisms to ciprofloxacin.
224

225 Reports from the laboratory providing results of the standard single-disk susceptibility test
226 with a 5-µg ciprofloxacin disk should be interpreted according to the following criteria:
227

228 For testing *Enterobacteriaceae*, *Enterococcus* species, *Pseudomonas aeruginosa*, and
229 *Staphylococcus* species:

230

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

231

232

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

233

234

235

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:

236

237

238

239

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	30 – 40
<i>Staphylococcus aureus</i>	ATCC 25923	22 – 30
<i>Pseudomonas aeruginosa</i>	ATCC 27853	25 - 33

240

241

INDICATIONS AND USAGE

242

CIPRO XR is indicated only for the treatment of urinary tract infections, including acute uncomplicated pyelonephritis, caused by susceptible strains of the designated microorganisms as listed below. CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

243

244

245

246

247

Uncomplicated Urinary Tract Infections (Acute Cystitis) caused by *Escherichia coli*, *Proteus mirabilis*, *Enterococcus faecalis*, or *Staphylococcus saprophyticus*^a.

248

249

250

Complicated Urinary Tract Infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, *Enterococcus faecalis*, *Proteus mirabilis*, or *Pseudomonas aeruginosa*^a.

251

252

253

Acute Uncomplicated Pyelonephritis caused by *Escherichia coli*.

254

255

^a Treatment of infections due to this organism in the organ system was studied in fewer than 10 patients.

256

257

258

THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING INFECTIONS OTHER THAN URINARY TRACT INFECTIONS HAS NOT BEEN DEMONSTRATED.

259

260

261

262

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 XR may be initiated before results of these tests are

263

264

265

266 known; once results become available appropriate therapy should be continued. Culture and
267 susceptibility testing performed periodically during therapy will provide information not only
268 on the therapeutic effect of the antimicrobial agent but also on the possible emergence of
269 bacterial resistance.

270

271 **CONTRAINDICATIONS**

272 CIPRO XR is contraindicated in persons with a history of hypersensitivity to ciprofloxacin or
273 any member of the quinolone class of antimicrobial agents.

274

275 **WARNINGS**

276 **THE SAFETY AND EFFECTIVENESS OF CIPRO XR IN PEDIATRIC PATIENTS**
277 **AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN,**
278 **AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED.** (See **PRECAUTIONS:**

279 **Pediatric Use, Pregnancy, and Nursing Mothers** subsections.) The oral administration of
280 ciprofloxacin caused lameness in immature dogs. Histopathological examination of the
281 weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related
282 quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other
283 signs of arthropathy in immature animals of various species. (See **ANIMAL**
284 **PHARMACOLOGY.**)

285

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

298

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

306

307 Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the
308 first dose, have been reported in patients receiving quinolone therapy. Some reactions were
309 accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial
310 edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity

311 reactions. Serious anaphylactic reactions require immediate emergency treatment with
312 epinephrine. Oxygen, intravenous steroids, and airway management, including intubation,
313 should be administered as indicated.

314

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

320

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

325

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

329

330 If a diagnosis of pseudomembranous colitis is established, therapeutic measures should be
331 initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation
332 alone. In moderate to severe cases, consideration should be given to management with fluids
333 and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically
334 effective against *C. difficile* colitis.

335

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

339

340 PRECAUTIONS

341

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

348

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

352

353 Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been
354 observed in patients who are exposed to direct sunlight while receiving some members of the

355 quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be
356 discontinued if phototoxicity occurs.

357

358 **Information for Patients:**

359 Patients should be advised:

360

361 ◆ that CIPRO XR may be taken with or without meals and to drink fluids liberally. As with
362 other quinolones, concurrent administration with magnesium/aluminum antacids, or
363 sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, or with
364 other products containing calcium, iron, or zinc should be avoided. CIPRO XR may be
365 taken two hours before or six hours after taking these products. (See **CLINICAL**
366 **PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND**
367 **ADMINISTRATION, and PRECAUTIONS, Drug Interactions.**) CIPRO XR should
368 not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone
369 since absorption of ciprofloxacin may be significantly reduced; however, CIPRO XR may
370 be taken with a meal that contains these products. (See **CLINICAL**
371 **PHARMACOLOGY, Drug-drug Interactions, DOSAGE AND**
372 **ADMINISTRATION, and PRECAUTIONS, Drug Interactions.**)

373

374 ◆ if the patient should forget to take CIPRO XR at the usual time, he/she may take the dose
375 later in the day. Do not take more than one CIPRO XR tablet per day even if a patient
376 misses a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR**
377 **CHEW THE TABLET.**

378

379 ◆ that ciprofloxacin may be associated with hypersensitivity reactions, even following a
380 single dose, and to discontinue CIPRO XR at the first sign of a skin rash or other allergic
381 reaction.

382

383 ◆ to avoid excessive sunlight or artificial ultraviolet light while receiving CIPRO XR and to
384 discontinue therapy if phototoxicity occurs.

385

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

388

389 ◆ that CIPRO XR may cause dizziness and lightheadedness; therefore, patients should
390 know how they react to this drug before they operate an automobile or machinery or
391 engage in activities requiring mental alertness or coordination.

392

393 ◆ that CIPRO XR may increase the effects of theophylline and caffeine. There is a
394 possibility of caffeine accumulation when products containing caffeine are consumed
395 while taking quinolones.

396

397 ♦ that convulsions have been reported in patients receiving quinolones, including
398 ciprofloxacin, and to notify their physician before taking CIPRO XR if there is a history
399 of this condition.
400

401 **Drug Interactions:** As with some other quinolones, concurrent administration of
402 ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline
403 and prolongation of its elimination half-life. This may result in increased risk of
404 theophylline-related adverse reactions. (See **WARNINGS**.) If concomitant use cannot be
405 avoided, serum levels of theophylline should be monitored and dosage adjustments made as
406 appropriate.
407

408 Some quinolones, including ciprofloxacin, have also been shown to interfere with the
409 metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of
410 its serum half-life.
411

412 Concurrent administration of a quinolone, including ciprofloxacin, with multivalent cation-
413 containing products such as magnesium/aluminum antacids, sucralfate, VIDEX®
414 (didanosine) chewable/buffered tablets or pediatric powder, or products containing calcium,
415 iron, or zinc may substantially interfere with the absorption of the quinolone, resulting in
416 serum and urine levels considerably lower than desired. CIPRO XR should be administered
417 at least 2 hours before or 6 hours after antacids containing magnesium or aluminum, as well
418 as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric powder, metal
419 cations such as iron, and multivitamin preparations with zinc. (See **CLINICAL**
420 **PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Information for**
421 **Patients, and DOSAGE AND ADMINISTRATION**.)
422

423 Histamine H₂-receptor antagonists appear to have no significant effect on the bioavailability
424 of ciprofloxacin.
425

426 Absorption of the CIPRO XR tablet was slightly diminished (20%) when given
427 concomitantly with omeprazole. (See **CLINICAL PHARMACOLOGY, Drug-drug**
428 **Interactions**.)
429

430 Altered serum levels of phenytoin (increased and decreased) have been reported in patients
431 receiving concomitant ciprofloxacin.
432

433 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has, on rare
434 occasions, resulted in severe hypoglycemia.
435

436 Some quinolones, including ciprofloxacin, have been associated with transient elevations in
437 serum creatinine in patients receiving cyclosporine concomitantly.
438

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

442

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

446

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

449

450 Salmonella/Microsome Test (Negative)

451 *E coli* DNA Repair Assay (Negative)

452 Mouse Lymphoma Cell Forward Mutation Assay (Positive)

453 Chinese Hamster V79 Cell HGPRT Test (Negative)

454 Syrian Hamster Embryo Cell Transformation Assay (Negative)

455 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)

456 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion

457 Assay (Negative)

458 Rat Hepatocyte DNA Repair Assay (Positive)

459

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

462

463 Rat Hepatocyte DNA Repair Assay

464 Micronucleus Test (Mice)

465 Dominant Lethal Test (Mice)

466

467 Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity studies with rats
468 and mice at daily oral dose levels of 250 and 750 mg/kg, respectively (approximately 2 and 3
469 -fold greater than the 1000 mg daily human dose based upon body surface area).

470 Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the
471 time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless
472 (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to
473 78 weeks while concurrently being administered ciprofloxacin. The time to development of
474 the first skin tumors was 50 weeks in mice treated concomitantly with UVA and
475 ciprofloxacin (mouse dose approximately equal to the maximum recommended daily human
476 dose of 1000 mg based upon mg/m^2), as opposed to 34 weeks when animals were treated with
477 both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks
478 in mice treated concomitantly with UVA and other quinolones.

479

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

483

484 Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg (1.0 times
485 the highest recommended daily human dose of 1000 mg based upon body surface area)
486 revealed no evidence of impairment.

487
488 **Pregnancy: Teratogenic Effects. Pregnancy Category C:** There are no adequate and
489 well-controlled studies in pregnant women. An expert review of published data on
490 experiences with ciprofloxacin use during pregnancy by TERIS - the Teratogen Information
491 System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial
492 teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state there
493 is no risk.

494
495 A controlled prospective observational study followed 200 women exposed to
496 fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during
497 gestation. In utero exposure to fluoroquinolones during embryogenesis was not associated
498 with increased risk of major malformations. The reported rates of major congenital
499 malformations were 2.2% for the fluoroquinolone group and 2.6% for the control group
500 (background incidence of major malformations is 1-5%). Rates of spontaneous abortions,
501 prematurity and low birth weight did not differ between the groups and there were no
502 clinically significant musculoskeletal dysfunctions up to one year of age in the ciprofloxacin
503 exposed children.

504
505 Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone
506 exposure (93% first trimester exposures). There were 70 ciprofloxacin exposures, all within
507 the first trimester. The malformation rates among live-born babies exposed to ciprofloxacin
508 and to fluoroquinolones overall were both within background incidence ranges. No specific
509 patterns of congenital abnormalities were found. The study did not reveal any clear adverse
510 reactions due to in utero exposure to ciprofloxacin.

511
512 No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen
513 in women exposed to ciprofloxacin during pregnancy. However, these small postmarketing
514 epidemiology studies, of which most experience is from short term, first trimester exposure,
515 are insufficient to evaluate the risk for the less common defects or to permit reliable and
516 definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their
517 developing fetuses. Ciprofloxacin should not be used during pregnancy unless potential
518 benefit justifies the potential risk to both fetus and mother (see **WARNINGS**).

519
520 Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg
521 (0.7 and 0.4 times the maximum daily human dose of 1000 mg based upon body surface area,
522 respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In
523 rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances
524 resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity
525 was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no
526 maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was
527 observed.

528
529 **Nursing Mothers:** Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin
530 absorbed by the nursing infant is unknown. Because of the potential for serious adverse
531 reactions in infants nursing from mothers taking ciprofloxacin, a decision should be made

532 whether to discontinue nursing or to discontinue the drug, taking into account the importance
533 of the drug to the mother.

534

535 **Pediatric Use:** Safety and effectiveness of CIPRO XR in pediatric patients and adolescents
536 less than 18 years of age have not been established. Ciprofloxacin causes arthropathy in
537 juvenile animals. (See **WARNINGS**.)

538

539 **Geriatric Use:** In a large, prospective, randomized CIPRO XR clinical trial in complicated
540 urinary tract infections, 49% (509/1035) of the patients were 65 and over, while 30%
541 (308/1035) were 75 and over. No overall differences in safety or effectiveness were observed
542 between these subjects and younger subjects, and clinical experience with other formulations
543 of ciprofloxacin has not identified differences in responses between the elderly and younger
544 patients, but greater sensitivity of some older individuals cannot be ruled out. Ciprofloxacin
545 is known to be substantially excreted by the kidney, and the risk of adverse reactions may be
546 greater in patients with impaired renal function. No alteration of dosage is necessary for
547 patients greater than 65 years of age with normal renal function. However, since some older
548 individuals experience reduced renal function by virtue of their advanced age, care should be
549 taken in dose selection for elderly patients, and renal function monitoring may be useful in
550 these patients. (See **CLINICAL PHARMACOLOGY** and **DOSAGE AND**
551 **ADMINISTRATION**.)

552

553 **ADVERSE REACTIONS**

554

555 Clinical trials in patients with urinary tract infections enrolled 961 patients treated with 500
556 mg or 1000 mg CIPRO XR. Most adverse events reported were described as mild to moderate
557 in severity and required no treatment. The overall incidence, type and distribution of adverse
558 events were similar in patients receiving both 500 mg and 1000 mg of CIPRO XR. Because
559 clinical trials are conducted under widely varying conditions, adverse reaction rates observed
560 in clinical trials of a drug cannot be directly compared to rates observed in clinical trials of
561 another drug and may not reflect the rates observed in practice. The adverse reaction
562 information from clinical studies does, however, provide a basis for identifying the adverse
563 events that appear to be related to drug use and for approximating rates.

564

565 In the clinical trial of uncomplicated urinary tract infection, CIPRO XR (500 mg once daily)
566 in 444 patients was compared to ciprofloxacin immediate-release tablets (250 mg twice daily)
567 in 447 patients for 3 days. Discontinuations due to adverse reactions thought to be drug-
568 related occurred in 0.2% (1/444) of patients in the CIPRO XR arm and in 0% (0/447) of
569 patients in the control arm.

570

571 In the clinical trial of complicated urinary tract infection and acute uncomplicated
572 pyelonephritis, CIPRO XR (1000 mg once daily) in 517 patients was compared to
573 ciprofloxacin immediate-release tablets (500 mg twice daily) in 518 patients for 7 to 14 days.
574 Discontinuations due to adverse reactions thought to be drug-related occurred in 3.1%
575 (16/517) of patients in the CIPRO XR arm and in 2.3% (12/518) of patients in the control
576 arm. The most common reasons for discontinuation in the CIPRO XR arm were

577 nausea/vomiting (4 patients) and dizziness (3 patients). In the control arm the most common
578 reason for discontinuation was nausea/vomiting (3 patients).

579

580 In these clinical trials, the following events occurred in $\geq 2\%$ of all CIPRO XR patients,
581 regardless of drug relationship : nausea (4%), headache (3%), dizziness (2%), diarrhea (2%),
582 vomiting (2%) and vaginal moniliasis (2%).

583

584 Adverse events, judged by investigators to be at least possibly drug-related, occurring in
585 greater than or equal to 1% of all CIPRO XR treated patients were: nausea (3%), diarrhea
586 (2%), headache (1%), dyspepsia (1%), dizziness (1%), and vaginal moniliasis (1%).
587 Vomiting (1%) occurred in the 1000 mg group.

588

589 Additional uncommon events, judged by investigators to be at least possibly drug-related,
590 that occurred in less than 1% of CIPRO XR treated patients were:

591

BODY AS A WHOLE: abdominal pain, asthenia, malaise, photosensitivity reaction

592

CARDIOVASCULAR: bradycardia, migraine, syncope

593

DIGESTIVE: anorexia, constipation, dry mouth, flatulence, liver function tests abnormal,
594 thirst

595

HEMIC/LYMPHATIC: prothrombin decreased

596

CENTRAL NERVOUS SYSTEM: abnormal dreams, depersonalization, depression,
597 hypertonia, incoordination, insomnia, somnolence, tremor, vertigo

598

METABOLIC: hyperglycemia

599

SKIN/APPENDAGES: dry skin, maculopapular rash, pruritus, rash, skin disorder,
600 urticaria, vesiculobullous rash

601

SPECIAL SENSES: diplopia, taste perversion

602

UROGENITAL: dysmenorrhea, hematuria, kidney function abnormal, vaginitis

603

604 The following additional adverse events, in alphabetical order, regardless of incidence or
605 relationship to drug, have been reported during clinical trials and from worldwide post-
606 marketing experience in patients given ciprofloxacin (includes all formulations, all dosages,
607 all drug-therapy durations, and all indications). Because these reactions have been reported
608 voluntarily from a population of uncertain size, it is not always possible to reliably estimate
609 their frequency or a causal relationship to drug exposure. The events are:

610

611 achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from urticaria to
612 anaphylactic reactions), anemia, angina pectoris, angioedema, anosmia, anxiety, arrhythmia,
613 arthralgia, ataxia, atrial flutter, bleeding diathesis, blurred vision, bronchospasm, *C difficile*
614 associated diarrhea, candidiasis (cutaneous, oral), candiduria, cardiac murmur,
615 cardiopulmonary arrest, cardiovascular collapse, cerebral thrombosis, chills, cholestatic
616 jaundice, confusion, convulsion, delirium, drowsiness, dysphagia, dysphasia, dyspnea, edema
617 (conjunctivae, face, hands, laryngeal, lips, lower extremities, neck, pulmonary), epistaxis,
618 erythema multiforme, erythema nodosum, exfoliative dermatitis, fever, flushing,
619 gastrointestinal bleeding, gout (flare up), gynecomastia, hallucinations, hearing loss,
620 hemolytic anemia, hemoptysis, hemorrhagic cystitis, hepatic necrosis, hiccup,
621 hyperpigmentation, hypertension, hypotension, ileus, interstitial nephritis, intestinal
perforation, jaundice, joint stiffness, lethargy, lightheadedness, lymphadenopathy, manic

622 reaction, myalgia, myasthenia gravis (possible exacerbation), myocardial infarction,
623 myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back, breast, chest,
624 epigastric, eye, foot, jaw, neck, oral mucosa), palpitation, pancreatitis, paranoia, paresthesia,
625 perspiration (increased), phobia, pleural effusion, polyuria, postural hypotension,
626 pseudomembranous colitis, pulmonary embolism, purpura, renal calculi, renal failure,
627 respiratory arrest, respiratory distress, restlessness, Stevens-Johnson syndrome, tachycardia,
628 taste loss, tendinitis, tendon rupture, tinnitus, toxic epidermal necrolysis, toxic psychosis,
629 unresponsiveness, urethral bleeding, urinary retention, urination (frequent), vaginal pruritus,
630 vasculitis, ventricular ectopy, vesicles, visual acuity (decreased), visual disturbances (flashing
631 lights, change in color perception, overbrightness of lights).

632

633 **Laboratory Changes:**

634

635 The following adverse laboratory changes, in alphabetical order, regardless of incidence or
636 relationship to drug, have been reported in patients given ciprofloxacin (includes all
637 formulations, all dosages, all drug-therapy durations, and all indications):

638

639 Decreases in blood glucose, BUN, hematocrit, hemoglobin, leukocyte counts, platelet counts,
640 prothrombin time, serum albumin, serum potassium, total serum protein, uric acid.

641

642 Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical lymphocyte counts,
643 blood glucose, blood monocytes, BUN, cholesterol, eosinophil counts, LDH, platelet counts,
644 prothrombin time, sedimentation rate, serum amylase, serum bilirubin, serum calcium, serum
645 cholesterol, serum creatine phosphokinase, serum creatinine, serum gamma-glutamyl
646 transpeptidase (GGT), serum potassium, serum theophylline (in patients receiving
647 theophylline concomitantly), serum triglycerides, uric acid.

648

649 Others: albuminuria, change in serum phenytoin, crystalluria, cylindruria, immature WBCs,
650 leukocytosis, methemoglobinemia, pancytopenia.

651

652 **OVERDOSAGE**

653 In the event of acute excessive overdosage, the stomach should be emptied by inducing
654 vomiting or by gastric lavage. The patient should be carefully observed and given supportive
655 treatment, including administration of magnesium or calcium containing antacids which can
656 reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a
657 small amount of ciprofloxacin (< 10%) is removed from the body after hemodialysis or
658 peritoneal dialysis.

659

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

662

663 Single doses of ciprofloxacin were relatively non-toxic via the oral route of administration in
664 mice, rats, and dogs. No deaths occurred within a 14-day post treatment observation period
665 at the highest oral doses tested; up to 5000 mg/kg in either rodent species, or up to 2500
666 mg/kg in the dog. Clinical signs observed included hypoactivity and cyanosis in both rodent

667 species and severe vomiting in dogs. In rabbits, significant mortality was seen at doses of
668 ciprofloxacin > 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days
669 after dosing.

670

671 **DOSAGE AND ADMINISTRATION**

672

673 CIPRO XR and ciprofloxacin immediate-release tablets are not interchangeable. Cipro XR
674 should be administered orally once daily as described in the following Dosage Guidelines
675 table:

676

677

678

DOSAGE GUIDELINES

<u>Indication</u>	<u>Unit Dose</u>	<u>Frequency</u>	<u>Usual Duration</u>
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days
Complicated Urinary Tract Infection	1000 mg	Q24h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000 mg	Q24h	7-14 Days

679

680 Patients whose therapy is started with CIPRO I.V. for urinary tract infections may be
681 switched to CIPRO XR when clinically indicated at the discretion of the physician.

682

683 CIPRO XR should be administered at least 2 hours before or 6 hours after antacids containing
684 magnesium or aluminum, as well as sucralfate, VIDEX® (didanosine) chewable/buffered
685 tablets or pediatric powder, metal cations such as iron, and multivitamin preparations with
686 zinc. Although CIPRO XR may be taken with meals that include milk, concomitant
687 administration with dairy products alone, or with calcium-fortified products should be
688 avoided, since decreased absorption is possible. A 2-hour window between substantial
689 calcium intake (> 800 mg) and dosing with CIPRO XR is recommended. CIPRO XR should
690 be swallowed whole. **DO NOT SPLIT, CRUSH, OR CHEW THE TABLET.** (See
691 **CLINICAL PHARMACOLOGY, Drug-drug Interactions, PRECAUTIONS, Drug**
692 **Interactions and Information for Patients.**)

693

694

Impaired Renal Function:

695

696

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 alternate pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving 500 mg CIPRO XR. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of < 30 mL/min, the dose of CIPRO XR should be reduced from 1000 mg to 500 mg daily. For patients on hemodialysis or peritoneal dialysis, administer CIPRO XR after the dialysis procedure is completed. (See **CLINICAL PHARMACOLOGY, Special Populations, and PRECAUTIONS, Geriatric Use.**)

706

707

Impaired Hepatic Function:

708

709

No dosage adjustment is required with CIPRO XR in patients with stable chronic cirrhosis. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated. (See **CLINICAL PHARMACOLOGY, Special Populations.**)

712

713

HOW SUPPLIED

714

CIPRO XR is available as nearly white to slightly yellowish, film-coated, oblong-shaped tablets containing 500 mg or 1000 mg ciprofloxacin. The 500 mg tablet is coded with the word "BAYER" on one side and "C500 QD" on the reverse side. The 1000 mg tablet is coded with the word "BAYER" on one side and "C1000 QD" on the reverse side.

718

719

	Strength	NDC Code
--	----------	----------

720

721

Bottles of 50	500 mg	0026-8889-50
---------------	--------	--------------

722

Bottles of 100	500 mg	0026-8889-51
----------------	--------	--------------

723

724

Bottles of 50	1000 mg	0026-8897-50
---------------	---------	--------------

725

Bottles of 100	1000 mg	0026-8897-51
----------------	---------	--------------

726

Unit Dose Pack of 30	1000 mg	0026-8897-69
----------------------	---------	--------------

727

728

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

730

731

ANIMAL PHARMACOLOGY

732

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.

737

738

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

746

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

750

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

753

754 **CLINICAL STUDIES**

755

756 **Uncomplicated Urinary Tract Infections (acute cystitis)**

757 CIPRO XR was evaluated for the treatment of uncomplicated urinary tract infections (acute
758 cystitis) in a randomized, double-blind, controlled clinical trial conducted in the US. This
759 study compared CIPRO XR (500 mg once daily for three days) with ciprofloxacin
760 immediate-release tablets (CIPRO® 250 mg BID for three days). Of the 905 patients
761 enrolled, 452 were randomly assigned to the CIPRO XR treatment group and 453 were
762 randomly assigned to the control group. The primary efficacy variable was bacteriologic
763 eradication of the baseline organism(s) with no new infection or superinfection at Test of
764 Cure (Day 4 - 11 Post-therapy).

765

766 The bacteriologic eradication and clinical success rates were similar between CIPRO XR and
767 the control group. The eradication and clinical success rates and their corresponding 95%
768 confidence intervals for the differences between rates (CIPRO XR minus control group are
769 given in the following table:

	CIPRO XR 500 mg QD x 3 Days	CIPRO 250 mg BID x 3 Days
Randomized Patients	452	453
Per Protocol Patients [†]	199	223
Bacteriologic Eradication at TOC (n/N)*	188/199 (94.5%)	209/223 (93.7%)
CI [-3.5%, 5.1%]		
Bacteriologic Eradication (by organism) at TOC (n/N)**		
<i>E coli</i>	156/160 (97.5%)	176/181 (97.2%)
<i>E faecalis</i>	10/11 (90.9%)	17/21 (81.0%)
<i>P mirabilis</i>	11/12 (91.7%)	7/7 (100%)
<i>S saprophyticus</i>	6/7 (85.7%)	9/9 (100%)
Clinical Response at TOC (n/N)***	189/199 (95.0%)	204/223 (91.5%)
CI [-1.1%, 8.1%]		

771 * n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total number of
772 patients

773 ** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

774 *** n/N = patients with clinical success /total number of patients

775 [†] The presence of a pathogen at a level of $\geq 10^5$ CFU/mL was required for microbiological evaluability criteria,
776 except for *S saprophyticus* ($\geq 10^4$ CFU/mL).

777

778 **Complicated Urinary Tract Infections and Acute Uncomplicated Pyelonephritis**

779

780 CIPRO XR was evaluated for the treatment of complicated urinary tract infections (cUTI)
781 and acute uncomplicated pyelonephritis (AUP) in a randomized, double-blind, controlled
782 clinical trial conducted in the US and Canada. The study enrolled 1,042 patients (521 patients
783 per treatment arm) and compared CIPRO XR (1000 mg once daily for 7 to 14 days) with
784 immediate-release ciprofloxacin (500 mg BID for 7 to 14 days). The primary efficacy
785 endpoint for this trial was bacteriologic eradication of the baseline organism(s) with no new
786 infection or superinfection at 5 to 11 days post-therapy (test-of-cure or TOC) for the Per
787 Protocol and Modified Intent-To-Treat (MITT) populations.

788

789 The Per Protocol population was defined as patients with a diagnosis of cUTI or AUP, a
790 causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, no inclusion criteria violation, a
791 valid test-of-cure urine culture within the TOC window, an organism susceptible to study
792 drug, no premature discontinuation or loss to follow-up, and compliance with the dosage
793 regimen (among other criteria). More patients in the CIPRO XR arm than in the control arm
794 were excluded from the Per Protocol population and this should be considered in the
795 interpretation of the study results. Reasons for exclusion with the greatest discrepancy
796 between the two arms were no valid test of cure urine culture, an organism resistant to the
797 study drug, and premature discontinuation due to adverse events.

798

799 An analysis of all patients with a causative organism(s) isolated at baseline and who received
800 study medication, defined as the MITT population, included 342 patients in the CIPRO XR
801 arm and 324 patients in the control arm. Patients with missing responses were counted as
802 failures in this analysis. In the MITT analysis of cUTI patients, bacteriologic eradication was
803 160/271 (59.0%) versus 156/248 (62.9%) in CIPRO XR and control arm, respectively [97.5%
804 CI* (-13.5%, 5.7%)]. Clinical cure was 184/271 (67.9%) for CIPRO XR and 182/248
805 (73.4%) for control arm, respectively [97.5% CI* (-14.4%, 3.5%)]. Bacterial eradication in
806 the MITT analysis of patients with AUP at TOC was 47/71 (66.2%) and 58/76 (76.3%) for
807 CIPRO XR and control arm, respectively [97.5% CI* (-26.8%, 6.5%)]. Clinical cure at TOC
808 was 50/71 (70.4%) for CIPRO XR and 58/76 (76.3%) for the control arm [97.5% CI* (-
809 22.0%, 10.4%)].

810

811 * confidence interval of the difference in rates (CIPRO XR minus control).

812

813 In the Per Protocol population, the differences between CIPRO XR and the control arm in
814 bacteriologic eradication rates at the TOC visit were not consistent between AUP and cUTI
815 patients. The bacteriologic eradication rate for cUTI patients was higher in the CIPRO XR
816 arm than in the control arm. For AUP patients, the bacteriologic eradication rate was lower
817 in the CIPRO XR arm than in the control arm. This inconsistency was not observed between
818 the two treatment groups for clinical cure rates. Clinical cure rates were 96.1% (198/206) and
819 92.1% (211/229) for CIPRO XR and the control arm, respectively.

820
821
822
823
824
825

The bacterial eradication and clinical cure rates by infection type for CIPRO XR and the control arm at the TOC visit and their corresponding 97.5% confidence intervals for the differences between rates (CIPRO XR minus control arm) are given below for the Per Protocol population analysis:

	CIPRO XR 1000 mg QD	CIPRO 500 mg BID
Randomized Patients	521	521
Per Protocol Patients [^]	206	229
cUTI Patients		
Bacteriologic Eradication at TOC (n/N)*	148/166 (89.2%)	144/177 (81.4%)
CI [-0.7%, 16.3%]		
Bacteriologic Eradication (by organism) at TOC (n/N)**		
<i>E coli</i>	91/94 (96.8%)	90/92 (97.8%)
<i>K pneumoniae</i>	20/21 (95.2%)	19/23 (82.6%)
<i>E faecalis</i>	17/17 (100%)	14/21 (66.7%)
<i>P mirabilis</i>	11/12 (91.6%)	10/10 (100%)
<i>P aeruginosa</i>	3/3 (100%)	3/3 (100%)
Clinical Cure at TOC (n/N)***	159/166 (95.8%)	161/177 (91.0%)
CI [-1.1%, 10.8%]		
AUP Patients		
Bacteriologic Eradication at TOC (n/N)*	35/40 (87.5%)	51/52 (98.1%)
CI [-34.8%, 6.2%]		
Bacteriologic Eradication of <i>E. coli</i> at TOC (n/N)**	35/36 (97.2%)	41/41 (100%)
Clinical Cure at TOC (n/N)***	39/40 (97.5%)	50/52 (96.2%)
CI [-15.3%, 21.1%]		

826 [^] Patients excluded from the Per Protocol population were primarily those with no causative organism(s) at
827 baseline or no organism present at $\geq 10^5$ CFU/mL at baseline, inclusion criteria violation, no valid test-of-cure
828 urine culture within the TOC window, an organism resistant to study drug, premature discontinuation due to an
829 adverse event, lost to follow-up, or non-compliance with dosage regimen (among other criteria).

830 * n/N = patients with baseline organism(s) eradicated and no new infections or superinfections/total
831 number of patients

832 ** n/N = patients with specified baseline organism eradicated/patients with specified baseline organism

833 *** n/N = patients with clinical success /total number of patients

834

835 Of the 166 cUTI patients treated with CIPRO XR, 148 (89%) had the causative organism(s)
836 eradicated, 8 (5%) had persistence, 5 (3%) patients developed superinfections and 5 (3%)
837 developed new infections. Of the 177 cUTI patients treated in the control arm, 144 (81%)
838 had the causative organism(s) eradicated, 16 (9%) patients had persistence, 3 (2%) developed
839 superinfections and 14 (8%) developed new infections. Of the 40 patients with AUP treated
840 with CIPRO XR, 35 (87.5%) had the causative organism(s) eradicated, 2 (5%) patients had

841 persistence and 3 (7.5%) developed new infections. Of the 5 CIPRO XR AUP patients
842 without eradication at TOC, 4 were considered clinical cures and did not receive alternative
843 antibiotic therapy. Of the 52 patients with AUP treated in the control arm, 51 (98%) had the
844 causative organism(s) eradicated. One patient (2%) had persistence.

845
846 **References:** 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility Tests for
847 Bacteria That Grow Aerobically-Sixth Edition. Approved Standard NCCLS Document M7-
848 A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January 2003.
849 2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-Eighth
850 Edition. Approved Standard NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne,
851 PA, January, 2003.

852

853 **PATIENT INFORMATION ABOUT CIPRO® XR**

854 **(ciprofloxacin extended-release tablets)**

855

856 This section contains important patient information about CIPRO XR and should be read
857 completely before you begin treatment. This section does not take the place of discussion
858 with your doctor or health care professional about your medical condition or your treatment.
859 This section does not list all benefits and risks of CIPRO XR. CIPRO XR can be prescribed
860 only by a licensed health care professional. Your doctor has prescribed CIPRO XR only for
861 you.

862
863 CIPRO XR is intended only to treat urinary tract infections and acute uncomplicated
864 pyelonephritis (also known as a kidney infection). It should not be used to treat other
865 infections. Do not give it to other people even if they have a similar condition. Do not use it
866 for a condition for which it was not prescribed. If you have any concerns about your
867 condition or your medicine, ask your doctor. Only your doctor can determine if CIPRO XR
868 is right for you.

869

870 **What is CIPRO XR?**

871

872 CIPRO XR is an antibiotic in the quinolone class that contains the active ingredient
873 ciprofloxacin. CIPRO XR is specifically formulated to be taken just once daily to kill
874 bacteria causing infection in the urinary tract. CIPRO XR has been shown in clinical trials to
875 be effective in the treatment of urinary tract infections. You should contact your doctor if
876 your condition is not improving while taking CIPRO XR.

877
878 CIPRO XR Tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets.
879 CIPRO XR is available in a 500 mg and 1000 mg tablet strengths.

880

881 **How and when should I take CIPRO XR?**

882

883 CIPRO XR should be taken once a day for three (3) to fourteen (14) days depending on your
884 infection. Take CIPRO XR at approximately the same time each day with food or on an
885 empty stomach. CIPRO XR should not be taken with dairy products (like milk or yogurt) or

886 calcium-fortified juices alone; however, CIPRO XR may be taken with a meal that contains
887 these products. Should you forget to take it at the usual time, you may take your dose later in
888 the day. Do not take more than one CIPRO XR tablet per day even if you missed a dose.
889 Swallow the CIPRO XR tablet whole. **DO NOT SPLIT, CRUSH, OR CHEW THE**
890 **TABLET.**

891
892 You should take CIPRO XR for as long as your doctor prescribes it, even after you start to
893 feel better. Stopping an antibiotic too early may result in failure to cure your infection.
894

895 **Who should not take CIPRO XR?**

896
897 You should not take CIPRO XR if you have ever had a severe reaction to any of the group of
898 antibiotics known as "quinolones."
899

900 CIPRO XR is not recommended for use during pregnancy or nursing, as the effects on the
901 unborn child or nursing infant are unknown. If you are pregnant or plan to become pregnant
902 while taking CIPRO XR, talk to your doctor before taking this medication.
903

904 CIPRO XR is not recommended for persons less than 18 years of age.
905

906 **What are the possible side effects of CIPRO XR?**

907 CIPRO XR is generally well tolerated. The most common side effects, which are usually
908 mild, include nausea, headache, dyspepsia, dizziness, vaginal yeast infection and diarrhea. If
909 diarrhea persists, call your health care professional. Antibiotics of the quinolone class may
910 also cause vomiting, rash, and abdominal pain/discomfort.
911

912 You should be careful about driving or operating machinery until you are sure CIPRO XR is
913 not causing dizziness.
914

915 Rare cases of allergic reactions have been reported in patients receiving quinolones, including
916 ciprofloxacin, even after just one dose. If you develop hives, difficulty breathing, or other
917 symptoms of a severe allergic reaction, seek emergency treatment right away. If you develop
918 a skin rash, you should stop taking CIPRO XR and call your health care professional.
919

920 Some patients taking quinolone antibiotics may become more sensitive to sunlight or
921 ultraviolet light such as that used in tanning salons. You should avoid excessive exposure to
922 sunlight or ultraviolet light while you are taking CIPRO XR.
923

924 Ciprofloxacin has been rarely associated with inflammation of tendons. If you experience
925 pain, swelling or rupture of a tendon, you should stop taking CIPRO XR and call your health
926 care professional.
927

928 Convulsions have been reported in patients receiving quinolone antibiotics including
929 ciprofloxacin. If you have experienced convulsions in the past, be sure to let your physician
930 know that you have a history of convulsions. Quinolones, including ciprofloxacin, have been

931 rarely associated with other central nervous system events including confusion, tremors,
932 hallucinations, and depression.

933

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

936

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

938

939 CIPRO XR can affect how other medicines work. Tell your doctor about all other
940 prescriptions and non-prescription medicines or supplements you are taking. This is
941 especially important if you are taking theophylline or VIDEX® (didanosine)
942 chewable/buffered tablets or pediatric powder. Other medications including warfarin,
943 glyburide, and phenytoin may also interact with CIPRO XR.

944

945 Many antacids, multivitamins, and other dietary supplements containing magnesium,
946 calcium, aluminum, iron or zinc can interfere with the absorption of CIPRO XR and may
947 prevent it from working. You should take CIPRO XR either 2 hours before or 6 hours after
948 taking these products.

949

950 **Remember:**

951

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

953

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

955

956 Keep CIPRO XR and all medications out of reach of children.

957

958 This information does not take the place of discussions with your doctor or health care
959 professional about your medication or treatment.

960

961 **Rx Only**

962

963 New Bayer Logo

964

Bayer Pharmaceuticals Corporation

965

400 Morgan Lane

966

West Haven, CT 06516

967

Made in Germany

968

969 Draft Bay o 9867/q 3939 8/03 © 2003 Bayer Pharmaceuticals Corporation Printed in
970 U.S.A.