

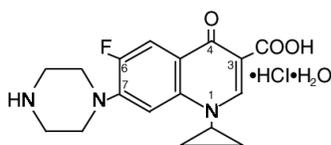
1 **CIPRO[®] XR**
2 **(ciprofloxacin* extended-release tablets)**

3
4 **Final uUTI PI**

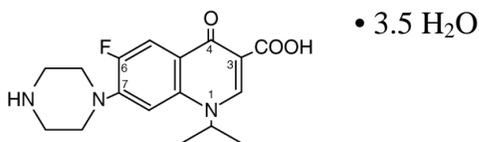
12/12/02

5
6 **DESCRIPTION**

7 CIPRO[®] XR (ciprofloxacin* extended-release tablets) contain ciprofloxacin, a
8 synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO
9 XR Tablets are coated, bilayer tablets consisting of an immediate-release layer
10 and an erosion-matrix type controlled-release layer. The tablets contain a
11 combination of two types of ciprofloxacin drug substance, ciprofloxacin
12 hydrochloride and ciprofloxacin betaine (base). Ciprofloxacin hydrochloride is
13 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-
14 quinolinecarboxylic acid hydrochloride. It is provided as a mixture of the
15 monohydrate and the sesquihydrate. The empirical formula of the monohydrate
16 is C₁₇H₁₈FN₃O₃ • HCl • H₂O and its molecular weight is 385.8. The empirical
17 formula of the sesquihydrate is C₁₇H₁₈FN₃O₃ • HCl • 1.5 H₂O and its molecular
18 weight is 394.8. The drug substance is a faintly yellowish to light yellow
19 crystalline substance. The chemical structure of the monohydrate is as follows:
20



21 Ciprofloxacin betaine is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-
22 piperazinyl)-3-quinolinecarboxylic acid. As a hydrate, its empirical formula is
23 C₁₇H₁₈FN₃O₃ • 3.5 H₂O and its molecular weight is 394.3. It is a pale yellowish
24 to light yellow crystalline substance and its chemical structure is as follows:
25
26



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

36
37 * as ciprofloxacin[†] and ciprofloxacin hydrochloride

38 † does not comply with the loss on drying test and residue on ignition test of the
39 USP monograph.
40

41 **CLINICAL PHARMACOLOGY**

42

43 **Absorption**

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

48

49 Maximum plasma ciprofloxacin concentrations are attained between 1 and 4
50 hours after dosing with CIPRO XR. In comparison to the 250 mg ciprofloxacin
51 immediate-release BID treatment, which is approved for the treatment of
52 uncomplicated urinary tract infections, the C_{max} of CIPRO XR 500mg once
53 daily is higher, while the AUC over 24 hours is equivalent.

54

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

58

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

	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)

61

§ median (range)

62

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

66

67 **Distribution**

68 The volume of distribution calculated for intravenous ciprofloxacin is
69 approximately 2.1 – 2.7 L/kg. Studies with the oral and intravenous forms of
70 ciprofloxacin have demonstrated penetration of ciprofloxacin into a variety of
71 tissues. The binding of ciprofloxacin to serum proteins is 20% to 40%, which is
72 not likely to be high enough to cause significant protein binding interactions
73 with other drugs. Following administration of a single dose of CIPRO XR,
74 ciprofloxacin concentrations in urine collected up to 4 hours after dosing
75 averaged over 300 mg/L; in urine excreted from 12 to 24 hours after dosing,
76 ciprofloxacin concentration averaged 27 mg/L.

77

78 **Metabolism**

79 Four metabolites of ciprofloxacin were identified in human urine. The
80 metabolites have antimicrobial activity, but are less active than unchanged
81 ciprofloxacin. The primary metabolites are oxociprofloxacin (M3) and
82 sulfociprofloxacin (M2), each accounting for roughly 3% to 8% of the total

83 dose. Other minor metabolites are desethylene ciprofloxacin (M1), and
84 formylciprofloxacin (M4). The relative proportion of drug and metabolite in
85 serum corresponds to the composition found in urine. Excretion of these
86 metabolites was essentially complete by 24 hours after dosing.

87

88 **Elimination**

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

107

108 **Special Populations**

109 Pharmacokinetic studies of the immediate-release oral tablet (single dose) and
110 intravenous (single and multiple dose) forms of ciprofloxacin indicate that
111 plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years)
112 as compared to young adults. C_{max} is increased 16% to 40%, and mean AUC is
113 increased approximately 30%, which can be at least partially attributed to
114 decreased renal clearance in the elderly. Elimination half-life is only slightly
115 (~20%) prolonged in the elderly. These differences are not considered clinically
116 significant. (See **PRECAUTIONS, Geriatric Use.**)

117

118 In patients with reduced renal function, the half-life of ciprofloxacin is slightly
119 prolonged. No dose adjustment is required for patients with uncomplicated
120 urinary tract infections receiving 500 mg CIPRO XR. The total drug exposure
121 attained with 500 mg CIPRO XR is similar to or less than that achieved with a
122 single dose of 500 mg immediate-release ciprofloxacin, which is approved for
123 use in patients with severe renal impairment. (See **DOSAGE AND**
124 **ADMINISTRATION.**)

125

126 In studies in patients with stable chronic cirrhosis, no significant changes in
127 ciprofloxacin pharmacokinetics have been observed. The kinetics of

128 ciprofloxacin in patients with acute hepatic insufficiency, however, have not
129 been fully elucidated (See **DOSAGE AND ADMINISTRATION**).

130

131 **Drug-drug Interactions**

132 Previous studies with immediate-release ciprofloxacin have shown that
133 concomitant administration of ciprofloxacin with theophylline decreases the
134 clearance of theophylline resulting in elevated serum theophylline levels and
135 increased risk of a patient developing CNS or other adverse reactions.

136 Ciprofloxacin also decreases caffeine clearance and inhibits the formation of
137 paraxanthine after caffeine administration. Absorption of ciprofloxacin is
138 significantly reduced by concomitant administration of multivalent cation-
139 containing products such as magnesium/aluminum antacids, sucralfate, Videx®
140 (didanosine) chewable/buffered tablets or pediatric powder, or products
141 containing calcium, iron, or zinc. (See **PRECAUTIONS, Drug Interactions**
142 **and Information for Patients**, and **DOSAGE AND ADMINISTRATION**.)

143

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

158

159 **Omeprazole:** When CIPRO XR was administered as a single 1000 mg dose
160 (twice the recommended daily dose) concomitantly with omeprazole (40 mg
161 once daily for three days) to 18 healthy volunteers, the mean AUC and C_{max} of
162 ciprofloxacin were reduced by 20% and 23%, respectively. (See
163 **PRECAUTIONS, Drug Interactions**.) These differences are not considered
164 clinically significant.

165

166 **MICROBIOLOGY**

167

168 Ciprofloxacin has *in vitro* activity against a wide range of gram-negative and
169 gram-positive organisms. The bactericidal action of ciprofloxacin results from
170 inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV (both Type
171 II topoisomerases), which are required for bacterial DNA replication,
172 transcription, repair, and recombination. The mechanism of action of

173 quinolones, including ciprofloxacin, is different from that of other antimicrobial
174 agents such as beta-lactams, macrolides, tetracyclines, or aminoglycosides;
175 therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.
176 There is no known cross-resistance between ciprofloxacin and other classes of
177 antimicrobials. Resistance to ciprofloxacin *in vitro* develops slowly (multiple-
178 step mutation). Resistance to ciprofloxacin due to spontaneous mutations occurs
179 at a general frequency of between $<10^{-9}$ to 1×10^{-6} .

180

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

185

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

188 **INDICATIONS AND USAGE** section.

189

Aerobic gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately
susceptible.)

Staphylococcus saprophyticus

190

Aerobic gram-negative microorganisms

Escherichia coli

Proteus mirabilis

191

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

194

195 Ciprofloxacin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1
196 $\mu\text{g/mL}$ or less against most ($\geq 90\%$) strains of the following microorganisms;
197 however, the safety and effectiveness of CIPRO XR in treating clinical
198 infections due to these microorganisms have not been established in adequate
199 and well-controlled clinical trials.

200

Aerobic gram-negative microorganisms

Citrobacter koseri

Klebsiella pneumoniae

Citrobacter freundii

Morganella morganii

Edwardsiella tarda

Proteus vulgaris

Enterobacter aerogenes

Providencia rettgeri

Enterobacter cloacae

Providencia stuartii

Klebsiella oxytoca

Serratia marcescens

201

Susceptibility Tests

202

203 **Dilution Techniques:** Quantitative methods are used to determine
204 antimicrobial minimal inhibitory concentrations (MICs). These MICs provide

205 estimates of the susceptibility of bacteria to antimicrobial compounds. The
206 MICs should be determined using a standardized procedure. Standardized
207 procedures are based on a dilution method¹ (broth or agar) or equivalent with
208 standardized inoculum concentrations and standardized concentrations of
209 ciprofloxacin. The MIC values should be interpreted according to the following
210 criteria:

211

212 For testing Enterobacteriaceae, *Enterococcus* species, and *Staphylococcus*
213 species:

214

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

215

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

228

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

232

<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

233

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

240

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

244 For testing Enterobacteriaceae, *Enterococcus* species, and *Staphylococcus*
245 species:

247

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

248

249 Interpretation should be as stated above for results using dilution techniques.

250 Interpretation involves correlation of the diameter obtained in the disk test with
251 the MIC for ciprofloxacin.

252

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

258

<u>Microorganism</u>		<u>Zone Diameter (mm)</u>
<i>Escherichia coli</i>	ATCC 25922	30 – 40
<i>Staphylococcus aureus</i>	ATCC 25923	22 – 30

259

260 **INDICATIONS AND USAGE**

261 CIPRO XR is indicated solely for the treatment of uncomplicated urinary tract
262 infections (acute cystitis) caused by susceptible strains of the designated
263 microorganisms as listed below. CIPRO XR and ciprofloxacin immediate-
264 release tablets are not interchangeable. Please see **DOSAGE AND**
265 **ADMINISTRATION** for specific recommendations.

266

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

270

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

273

274 **THE SAFETY AND EFFICACY OF CIPRO XR IN TREATING**
275 **INFECTIONS OTHER THAN UNCOMPLICATED URINARY TRACT**
276 **INFECTIONS HAVE NOT BEEN DEMONSTRATED.**

277

278 Appropriate culture and susceptibility tests should be performed before
279 treatment in order to isolate and identify organisms causing infection and to
280 determine their susceptibility to ciprofloxacin. Therapy with CIPRO XR may be
281 initiated before results of these tests are known; once results become available
282 appropriate therapy should be continued. Culture and susceptibility testing
283 performed periodically during therapy will provide information not only on the
284 therapeutic effect of the antimicrobial agent but also on the possible emergence
285 of bacterial resistance.

286

287 **CONTRAINDICATIONS**

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

290

291 **WARNINGS**

292 **THE SAFETY AND EFFECTIVENESS OF CIPRO XR IN PEDIATRIC**
293 **PATIENTS AND ADOLESCENTS (UNDER THE AGE OF 18 YEARS),**

294 **PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN**
295 **ESTABLISHED.** (See **PRECAUTIONS: Pediatric Use, Pregnancy, and**

296 **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused
297 lameness in immature dogs. Histopathological examination of the weight-
298 bearing joints of these dogs revealed permanent lesions of the cartilage. Related
299 quinolone-class drugs also produce erosions of cartilage of weight-bearing joints
300 and other signs of arthropathy in immature animals of various species. (See
301 **ANIMAL PHARMACOLOGY.**)

302

303 Convulsions, increased intracranial pressure, and toxic psychosis have been
304 reported in patients receiving quinolones, including ciprofloxacin.

305 Ciprofloxacin may also cause central nervous system (CNS) events including:
306 dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal
307 thoughts or acts. These reactions may occur following the first dose. If these
308 reactions occur in patients receiving ciprofloxacin, the drug should be
309 discontinued and appropriate measures instituted. As with all quinolones,
310 ciprofloxacin should be used with caution in patients with known or suspected
311 CNS disorders that may predispose to seizures or lower the seizure threshold
312 (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk
313 factors that may predispose to seizures or lower the seizure threshold (e.g.
314 certain drug therapy, renal dysfunction). (See **PRECAUTIONS: General,**
315 **Information for Patients, Drug Interactions** and **ADVERSE**
316 **REACTIONS.**)

317

318 **SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN**
319 **PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF**

320 **CIPROFLOXACIN AND THEOPHYLLINE.** These reactions have included
321 cardiac arrest, seizure, status epilepticus, and respiratory failure. Although
322 similar serious adverse effects have been reported in patients receiving
323 theophylline alone, the possibility that these reactions may be potentiated by

324 ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided,
325 serum levels of theophylline should be monitored and dosage adjustments made
326 as appropriate.

327

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

336

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

343

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

349

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

353

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

360

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

365

366 PRECAUTIONS

367

368 **General:** Crystals of ciprofloxacin have been observed rarely in the urine of
369 human subjects but more frequently in the urine of laboratory animals, which is

370 usually alkaline. (See **ANIMAL PHARMACOLOGY**.) Crystalluria related to
371 ciprofloxacin has been reported only rarely in humans because human urine is
372 usually acidic. Alkalinity of the urine should be avoided in patients receiving
373 ciprofloxacin. Patients should be well hydrated to prevent the formation of
374 highly concentrated urine.

375

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

380

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

385

386 **Information for Patients:**

387 Patients should be advised:

388

389 ◆ that CIPRO XR may be taken with or without meals and to drink fluids
390 liberally. As with other quinolones, concurrent administration with
391 magnesium/aluminum antacids, or sucralfate, VIDEX® (didanosine)
392 chewable/buffered tablets or pediatric powder, or with other products
393 containing calcium, iron, or zinc should be avoided. CIPRO XR may be
394 taken two hours before or six hours after taking these products. (See
395 **CLINICAL PHARMACOLOGY, Drug-drug Interactions, DOSAGE**
396 **AND ADMINISTRATION, and PRECAUTIONS, Drug Interactions**.)
397 CIPRO XR should not be taken with dairy products (like milk or yogurt) or
398 calcium-fortified juices alone since absorption of ciprofloxacin may be
399 significantly reduced; however, CIPRO XR may be taken with a meal that
400 contains these products. (See **CLINICAL PHARMACOLOGY, Drug-**
401 **drug Interactions, DOSAGE AND ADMINISTRATION, and**
402 **PRECAUTIONS, Drug Interactions**.)

403

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

408

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

412

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

415

- 416 ◆ that if they experience pain, inflammation, or rupture of a tendon to
417 discontinue treatment, to inform their physician, and to rest and refrain from
418 exercise.
- 419
- 420 ◆ that CIPRO XR may cause dizziness and lightheadedness; therefore, patients
421 should know how they react to this drug before they operate an automobile
422 or machinery or engage in activities requiring mental alertness or
423 coordination.
- 424
- 425 ◆ that CIPRO XR may increase the effects of theophylline and caffeine. There
426 is a possibility of caffeine accumulation when products containing caffeine
427 are consumed while taking quinolones.
- 428
- 429 ◆ that convulsions have been reported in patients receiving quinolones,
430 including ciprofloxacin, and to notify their physician before taking CIPRO
431 XR if there is a history of this condition.
- 432

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

439

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

443

444 Concurrent administration of a quinolone, including ciprofloxacin, with
445 multivalent cation-containing products such as magnesium/aluminum antacids,
446 sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric
447 powder, or products containing calcium, iron, or zinc may substantially interfere
448 with the absorption of the quinolone, resulting in serum and urine levels
449 considerably lower than desired. CIPRO XR should be administered at least 2
450 hours before or 6 hours after antacids containing magnesium or aluminum, as
451 well as sucralfate, VIDEX® (didanosine) chewable/buffered tablets or pediatric
452 powder, metal cations such as iron, and multivitamin preparations with zinc.
453 (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions,**
454 **PRECAUTIONS, Information for Patients, and DOSAGE AND**
455 **ADMINISTRATION**.)

456

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

459

460 Absorption of the CIPRO XR tablet was slightly diminished (20%) when given
461 concomitantly with omeprazole. This difference is not considered clinically

462 significant. (See **CLINICAL PHARMACOLOGY, Drug-drug**
463 **Interactions.**)

464
465 Altered serum levels of phenytoin (increased and decreased) have been reported
466 in patients receiving concomitant ciprofloxacin.

467
468 The concomitant administration of ciprofloxacin with the sulfonylurea glyburide
469 has, on rare occasions, resulted in severe hypoglycemia.

470
471 Some quinolones, including ciprofloxacin, have been associated with transient
472 elevations in serum creatinine in patients receiving cyclosporine concomitantly.

473
474 Quinolones have been reported to enhance the effects of the oral anticoagulant
475 warfarin or its derivatives. When these products are administered
476 concomitantly, prothrombin time or other suitable coagulation tests should be
477 closely monitored.

478
479 Probenecid interferes with renal tubular secretion of ciprofloxacin and produces
480 an increase in the level of ciprofloxacin in the serum. This should be considered
481 if patients are receiving both drugs concomitantly.

482
483 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Eight *in vitro*
484 mutagenicity tests have been conducted with ciprofloxacin, and the test results
485 are listed below:

486
487 Salmonella/Microsome Test (Negative)
488 *E. coli* DNA Repair Assay (Negative)
489 Mouse Lymphoma Cell Forward Mutation Assay (Positive)
490 Chinese Hamster V79 Cell HGPRT Test (Negative)
491 Syrian Hamster Embryo Cell Transformation Assay (Negative)
492 *Saccharomyces cerevisiae* Point Mutation Assay (Negative)
493 *Saccharomyces cerevisiae* Mitotic Crossover and Gene Conversion
494 Assay (Negative)
495 Rat Hepatocyte DNA Repair Assay (Positive)

496
497 Thus, 2 of the 8 tests were positive, but results of the following 3 *in vivo* test
498 systems gave negative results:

499
500 Rat Hepatocyte DNA Repair Assay
501 Micronucleus Test (Mice)
502 Dominant Lethal Test (Mice)

503
504 Ciprofloxacin was not carcinogenic or tumorigenic in 2-year carcinogenicity
505 studies with rats and mice at daily oral dose levels of 250 and 750 mg/kg,
506 respectively (approximately 4- and 6-fold greater than the 500 mg daily human
507 dose based upon body surface area).

508

509 Results from photo co-carcinogenicity testing indicate that ciprofloxacin does
510 not reduce the time to appearance of UV-induced skin tumors as compared to
511 vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours
512 five times every two weeks for up to 78 weeks while concurrently being
513 administered ciprofloxacin. The time to development of the first skin tumors
514 was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin
515 (mouse dose approximately twice the maximum recommended daily human
516 dose of 500 mg based upon mg/m^2), as opposed to 34 weeks when animals were
517 treated with both UVA and vehicle. The times to development of skin tumors
518 ranged from 16-32 weeks in mice treated concomitantly with UVA and other
519 quinolones.

520

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

525

526 Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg
527 (1.9 times the highest recommended daily human dose of 500 mg based upon
528 body surface area) revealed no evidence of impairment.

529

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

536

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

547

548 Another prospective follow-up study reported on 549 pregnancies with
549 fluoroquinolone exposure (93% first trimester exposures). There were 70
550 ciprofloxacin exposures, all within the first trimester. The malformation rates
551 among live-born babies exposed to ciprofloxacin and to fluoroquinolones
552 overall were both within background incidence ranges. No specific patterns of

553 congenital abnormalities were found. The study did not reveal any clear adverse
554 reactions due to in utero exposure to ciprofloxacin.

555

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

565

566 Reproduction studies have been performed in rats and mice using oral doses up
567 to 100 mg/kg (1.4 and 0.7 times the maximum daily human dose of 500 mg
568 based upon body surface area, respectively) and have revealed no evidence of
569 harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100
570 mg/kg orally) produced gastrointestinal disturbances resulting in maternal
571 weight loss and an increased incidence of abortion, but no teratogenicity was
572 observed at either dose. After intravenous administration of doses up to 20
573 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity
574 or teratogenicity was observed.

575

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

582

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

586

587 **Geriatric Use:** In clinical studies with immediate-release ciprofloxacin, no
588 differences in safety or effectiveness were observed between elderly and young
589 patients. Ciprofloxacin is substantially excreted by the kidney, and the risk of
590 adverse reactions may be greater in patients with impaired renal function.
591 However, no significant accumulation of ciprofloxacin is anticipated in elderly
592 subjects with renal impairment who take CIPRO XR. The total drug exposure
593 and maximum serum concentrations attained with CIPRO XR are similar to or
594 less than the corresponding values achieved with 500 mg immediate-release
595 ciprofloxacin, which is approved for use in renally impaired patients. Therefore,
596 no reductions in dosage are required. (See **CLINICAL PHARMACOLOGY**
597 and **DOSAGE AND ADMINISTRATION**.)

598

599 **ADVERSE REACTIONS**

600

601 A clinical trial enrolled 905 ciprofloxacin treated patients, of whom 444 patients
602 received the CIPRO XR 500 mg QD dose and 447 patients received the CIPRO
603 250 mg BID dose. Most adverse events reported (93.5%) were described as
604 mild to moderate in severity and required no treatment. CIPRO XR was
605 discontinued due to adverse reactions thought to be drug-related in 0.2% of
606 patients.

607

608 Adverse reactions, judged by investigators to be at least possibly drug-related,
609 occurring in greater than or equal to 1% of CIPRO XR treated patients were
610 nausea (3%) and headache (2%).

611

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

614 BODY AS A WHOLE: abdominal pain, photosensitivity reaction

615 CARDIOVASCULAR: migraine

616 DIGESTIVE: anorexia, constipation, diarrhea, dyspepsia, flatulence, thirst,
617 vomiting

618 CENTRAL NERVOUS SYSTEM: depersonalization, dizziness, hypertonia,
619 incoordination, somnolence

620 SKIN/APPENDAGES: maculopapular rash, pruritus, rash, skin disorder,
621 vesiculobullous rash

622 SPECIAL SENSES: taste perversion

623 UROGENITAL: dysmenorrhea, vaginal candidiasis, vaginitis

624

625 The following additional adverse events, in alphabetical order, regardless of
626 incidence or relationship to drug, have been reported during clinical trials and
627 from worldwide post-marketing experience in patients given ciprofloxacin
628 (includes all formulations, all dosages, all drug-therapy durations, and all
629 indications):

630 achiness, acidosis, agitation, agranulocytosis, allergic reactions (ranging from
631 urticaria to anaphylactic reactions), anemia, angina pectoris, angioedema,
632 anosmia, anxiety, arrhythmia, arthralgia, ataxia, atrial flutter, bleeding diathesis,
633 blurred vision, bronchospasm, *C. difficile* associated diarrhea, candidiasis
634 (cutaneous, oral), candiduria, cardiac murmur, cardiopulmonary arrest,
635 cardiovascular collapse, cerebral thrombosis, chills, cholestatic jaundice,
636 confusion, convulsion, delirium, depression, diplopia, drowsiness, dysphagia,
637 dysphasia, dyspnea, edema (conjunctivae, face, hands, laryngeal, lips, lower
638 extremities, neck, pulmonary), epistaxis, erythema multiforme, erythema
639 nodosum, exfoliative dermatitis, fever, flushing, gastrointestinal bleeding, gout
640 (flare up), gynecomastia, hallucinations, hearing loss, hematuria, hemolytic
641 anemia, hemoptysis, hemorrhagic cystitis, hepatic necrosis, hiccup,
642 hyperpigmentation, hypertension, hypotension, ileus, insomnia, interstitial
643 nephritis, intestinal perforation, jaundice, joint stiffness, lethargy,
644 lightheadedness, lymphadenopathy, malaise, manic reaction, mouth dryness,

645 myalgia, myasthenia gravis (possible exacerbation), myocardial infarction,
646 myoclonus, nephritis, nightmares, nystagmus, oral ulceration, pain (arm, back,
647 breast, chest, epigastric, eye, foot, jaw, neck, oral mucosa), palpitation,
648 pancreatitis, paranoia, paresthesia, perspiration (increased), phobia, pleural
649 effusion, polyuria, postural hypotension, pseudomembranous colitis, pulmonary
650 embolism, purpura, renal calculi, renal failure, respiratory arrest, respiratory
651 distress, restlessness, Stevens-Johnson syndrome, syncope, tachycardia, taste
652 loss, tendinitis, tendon rupture, tinnitus, toxic epidermal necrolysis, toxic
653 psychosis, tremor, unresponsiveness, urethral bleeding, urinary retention,
654 urination (frequent), vaginal pruritus, vasculitis, ventricular ectopy, vesicles,
655 visual acuity (decreased), visual disturbances (flashing lights, change in color
656 perception, overbrightness of lights), weakness.

657

658 **Laboratory Changes:**

659

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

664

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

668

669 Increases in alkaline phosphatase, ALT (SGPT), AST (SGOT), atypical
670 lymphocyte counts, blood glucose, blood monocytes, BUN, cholesterol,
671 eosinophil counts, LDH, platelet counts, prothrombin time, sedimentation rate,
672 serum amylase, serum bilirubin, serum calcium, serum cholesterol, serum
673 creatine phosphokinase, serum creatinine, serum gamma-glutamyl
674 transpeptidase (GGT), serum potassium, serum theophylline (in patients
675 receiving theophylline concomitantly), serum triglycerides, uric acid.

676

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

679

680 **OVERDOSAGE**

681 In the event of acute excessive overdose, the stomach should be emptied by
682 inducing vomiting or by gastric lavage. The patient should be carefully
683 observed and given supportive treatment. Adequate hydration must be
684 maintained. Only a small amount of ciprofloxacin (<10%) is removed from the
685 body after hemodialysis or peritoneal dialysis.

686

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

690

691 Single doses of ciprofloxacin were relatively non-toxic via the oral route of
692 administration in mice, rats, and dogs. No deaths occurred within a 14-day post
693 treatment observation period at the highest oral doses tested; up to 5000 mg/kg
694 in either rodent species, or up to 2500 mg/kg in the dog. Clinical signs observed
695 included hypoactivity and cyanosis in both rodent species and severe vomiting
696 in dogs. In rabbits, significant mortality was seen at doses of ciprofloxacin >
697 2500 mg/kg. Mortality was delayed in these animals, occurring 10-14 days after
698 dosing.

699

700 **DOSAGE AND ADMINISTRATION**

701

702 In uncomplicated urinary tract infections (acute cystitis), the recommended
703 dosage of CIPRO XR is 500 mg once daily for 3 days. CIPRO XR and
704 ciprofloxacin immediate-release tablets are not interchangeable.

705

706

706 **DOSAGE GUIDELINES**

707

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500 mg	Q24h	3 Days

708

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

720

721 **Impaired Renal Function:**

722

723 Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is
724 also metabolized and partially cleared through the biliary system of the liver and
725 through the intestine. These alternate pathways of drug elimination appear to
726 compensate for the reduced renal excretion in patients with renal impairment.
727 No dosage adjustment is required for patients with uncomplicated urinary tract
728 infections receiving 500 mg CIPRO XR. For patients on hemodialysis or
729 peritoneal dialysis, administer CIPRO XR after the dialysis procedure is
730 completed. (See **CLINICAL PHARMACOLOGY, Special Populations,**
731 **and PRECAUTIONS, Geriatric Use.**)

732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777

Impaired Hepatic Function:

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.**)

HOW SUPPLIED

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

	NDC Code
Bottles of 50	0026-8889-50
Bottles of 100	0026-8889-51

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

ANIMAL PHARMACOLOGY

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

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

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

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

778 **CLINICAL STUDIES**

779

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

781 CIPRO XR was evaluated for the treatment of uncomplicated urinary tract
 782 infections (acute cystitis) in a randomized, double-blind, controlled clinical trial
 783 conducted in the US. This study compared CIPRO XR (500 mg once daily for
 784 three days) with ciprofloxacin immediate-release tablets (Cipro 250 mg BID for
 785 three days). Of the 905 patients enrolled, 452 were randomly assigned to the
 786 CIPRO XR treatment group and 453 were randomly assigned to the control
 787 group. The primary efficacy variable was bacteriological eradication at Test of
 788 Cure (Day 4 – 11 Post-therapy).

789

790 The bacteriologic eradication and clinical success rates were similar between
 791 CIPRO XR and the control group. The eradication and clinical success rates and
 792 their corresponding 95% confidence intervals for the differences between rates
 793 (CIPRO XR minus control group) are given in the following table:

794

	CIPRO XR 500 mg QD x 3 Days	Cipro 250 mg BID x 3 Days
Randomized Patients	452	453
Per Protocol Patients [†]	199	223
Clinical Response at TOC (n/N)*	189/199 (95.0%)	204/223 (91.5%)
	CI [-1.1%, 8.1%]	
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%)

795

* n/N = patients with pathogen eradicated /total number of patients

796

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

798

799 **References:** 1. NCCLS, Methods for Dilution Antimicrobial Susceptibility
 800 Tests for Bacteria That Grow Aerobically-Fifth Edition. Approved Standard
 801 NCCLS Document M7-A5, Vol. 20, No. 2, NCCLS, Wayne, PA, January 2000.
 802 2. NCCLS, Performance Standards for Antimicrobial Disk Susceptibility Tests-
 803 Seventh Edition. Approved Standard NCCLS Document M2-A7, Vol. 20, No.
 804 1, NCCLS, Wayne, PA, January, 2000.

805

806 **PATIENT INFORMATION ABOUT CIPRO® XR**
807 **(ciprofloxacin extended-release tablets)**

808

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

815

816 CIPRO XR is intended only to treat simple urinary tract infections (also known
817 as cystitis or bladder infections). It should not be used to treat infections other
818 than simple urinary tract infections. Do not give it to other people even if they
819 have a similar condition. Do not use it for a condition for which it was not
820 prescribed. If you have any concerns about your condition or your medicine,
821 ask your doctor. Only your doctor can determine if CIPRO XR is right for you.

822

823 **What is CIPRO XR?**

824

825 CIPRO XR is an antibiotic in the quinolone class that contains the active
826 ingredient ciprofloxacin. CIPRO XR is specifically formulated to be taken just
827 once daily to kill bacteria causing simple urinary tract infections. CIPRO XR
828 has been shown in clinical trials to be effective in the treatment of simple
829 urinary tract infections. You should contact your doctor if your condition is not
830 improving while taking CIPRO XR.

831

832 CIPRO XR Tablets are nearly white to slightly yellowish, film-coated, oblong-
833 shaped tablets. CIPRO XR Tablets are available in a 500 mg strength.

834

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

836

837 CIPRO XR should be taken once a day for three (3) days at approximately the
838 same time each day with food or on an empty stomach. CIPRO XR should not
839 be taken with dairy products (like milk or yogurt) or calcium-fortified juices
840 alone; however, CIPRO XR may be taken with a meal that contains these
841 products. Should you forget to take it at the usual time, you may take your dose
842 later in the day. Do not take more than one CIPRO XR tablet per day even if
843 you missed a dose. Swallow the CIPRO XR tablet whole. **DO NOT SPLIT,**
844 **CRUSH, OR CHEW THE TABLET.**

845

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

849

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

851

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

854

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

859

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

861

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

863

864 CIPRO XR is generally well tolerated. The most common side effects, which
865 are usually mild, include nausea and headache. Antibiotics of the quinolone
866 class may also cause diarrhea, vomiting, rash, and abdominal pain/discomfort.
867 If diarrhea persists, call your health care professional.

868

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

871

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

877

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

882

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

886

887 Convulsions have been reported in patients receiving quinolone antibiotics
888 including ciprofloxacin. If you have experienced convulsions in the past, be
889 sure to let your physician know that you have a history of convulsions.
890 Quinolones, including ciprofloxacin, have been rarely associated with other
891 central nervous system events including confusion, tremors, hallucinations, and
892 depression.

893

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

897

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

899

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

905

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

910

911 **Remember:**

912

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

915

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

917

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

919

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

922

923 **Rx Only**

924

925 Draft Bay o 9867/q 3939 12/02 © 2002 Bayer Corporation Printed in
926 U.S.A.