Attachment 5

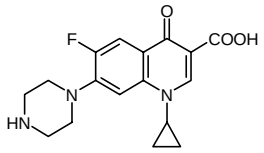
Reprint of Cipro® IV Label

CIPRO® I.V.
(ciprofloxacin)
For Intravenous Infusion

05/00

DESCRIPTION

CIPRO® I.V. (ciprofloxacin) is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is:



Ciprofloxacin

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

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

Parameters	500 mg q12h, P.O.	400 mg 12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC (µg●hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max}(µg/mL)	2.97	4.56	3.59	4.07

[a] AUC_{0-12h} [b] $AUC_{24h}=AUC_{0-12h}x2$ [c] $AUC_{24h}=AUC_{0-8h}x3$

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

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

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

Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (<1%) is recovered from the bile as unchanged drug. Approximately 15% of an I.V. dose is recovered from the feces within 5 days after dosing.

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

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

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

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

Following infusion of 400 mg I.V. ciprofloxacin every eight hours in combination with 50 mg/kg I.V. piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 μg/mL ½ hour and 1.18 μg/mL between 6-8 hours after the end of infusion.

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

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

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

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

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

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin susceptible)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

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

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin susceptible)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms

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

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

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

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms

Acinetobacter Iwoffi	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	*Vibrio cholerae*
Enterobacter aerogenes	*Vibrio parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella pneumophila	*Yersinia enterocolitica*

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

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

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

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

Susceptibility Tests

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

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [b]:

MIC (µg/mL)	Interpretation
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

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

For testing *Neisseria gonorrhoeae* [c]:

MIC (µg/mL)	Interpretation
≤ 0.06	Susceptible (S)

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

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

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

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

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

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

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

Zone Diameter (mm)	**Interpretation**
≥21	Susceptible (S)
16-20	Intermediate (I)
≤15	Resistant (R)

[a] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	**Interpretation**
≥21	Susceptible (S)

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

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

For testing *Neisseria gonorrhoeae* [c]:

Zone Diameter (mm)	Interpretation
≥36	Susceptible (S)

[c] This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

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

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

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

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

[a]These quality control limits are applicable to only *H. influenzae* ATCC 49247 testing using *Haemophilus* Test Medium (HTM)[1].

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

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLINICAL STUDIES

EMPIRICAL THERAPY IN FEBRILE NEUTROPENIC PATIENTS

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

The demographics of the evaluable patients were as follows:

Total	**Ciprofloxacin/Piperacillin N=233**	**Tobramycin/Piperacillin N=237**
Median Age (years)	47.0 (range 19-84)	50.0 (range 18-81)
Male	114 (48.9%)	117 (49.4%)
Female	119 (51.1%)	120 (50.6%)
Leukemia/Bone Marrow Transplant	165 (70.8%)	158 (66.7%)
Solid Tumor/Lymphoma	68 (29.2%)	79 (33.3%)
Median Duration of Neutropenia (days)	15.0 (range 1-61)	14.0 (range 1-89)

Clinical response rates observed in this study were as follows:

Outcomes	Ciprofloxacin/Piperacillin N=233 Success (%)	Tobramycin/Piperacillin N=237 Success (%)
Clinical Resolution of Initial Febrile Episode with No Modifications of Empirical Regimen*	63 (27.0%)	52 (21.9%)
Clinical Resolution of Initial Febrile Episode Including Patients with Modifications of Empirical Regimen	187 (80.3%)	185 (78.1%)
Overall Survival	224 (96.1%)	223 (94.1%)

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

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

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

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

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumors as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumors was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose

approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones.[3]

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

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

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

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

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

Short-term safety data from a single trial in pediatric cystic fibrosis patients are available. In a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5-17 years), 67 patients received ciprofloxacin I.V. 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10-21 days treatment and 62 patients received the combination of ceftazidime I.V. 50 mg/kg/dose q8h and tobramycin I.V. 3 mg/kg/dose q8h for a total of 10 - 21 days. Patients less than 5

years of age were not studied. Safety monitoring in the study included periodic range of motion examinations and gait assessments by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0-93 days). This study was not designed to determine long term effects and the safety of repeated exposure to ciprofloxacin.

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

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

ADVERSE REACTIONS

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

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

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

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris

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

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

I.V. INFUSION SITE: thrombophlebitis, burning, pain, pruritus, paresthesia, erythema, swelling

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

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

RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough

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

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

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

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

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

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

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

BODY AS A WHOLE: change in serum phenytoin
CARDIOVASCULAR: postural hypotension, vasculitis
CENTRAL NERVOUSE SYSTEM: agitation, delirium, myoclonus, toxic psychosis
HEMIC/LYMPHATIC: hemolytic anemia, methemoglobinemia
METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium
MUSCULOSKELETAL: myalgia, tendinitis/tendon rupture
RENAL/UROGENITAL: vaginal candidiasis
(See **PRECAUTIONS**.)

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

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

Other changes occurring infrequently were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation

of serum gamma-glutamyl transpeptidase (gamma GT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol.

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

OVERDOSAGE

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

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

DOSAGE AND ADMINSTRATION

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

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

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

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

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

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

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

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

DOSAGE GUIDELINES
Intravenous

Infection†	Type or Severity	Unit Dose	Frequency	Daily Dose
Urinary Tract	Mild/Moderate	200 mg	q12h	400 mg
	Severe/Complicated	400 mg	q12h	800 mg
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	1200 mg
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg
Bone and Joint	Mild/Moderate	400 mg	q12h	800 mg
	Severe/Complicated	400 mg	q8h	1200 mg
Intra-Abdominal*	Complicated	400 mg	q12h	800 mg
Acute Sinusitis	Mild/Moderate	400 mg	q12h	800 mg
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	800 mg
Empirical Therapy in Febrile Neutropenic Patients	Severe			
	Ciprofloxacin	400 mg	q8h	1200 mg
	+			
	Piperacillin	50 mg/kg	q4h	Not to exceed 24 g/day

* used in conjunction with metronidazole. (See product labeling for prescribing information.)
†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE**.)

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

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

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

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

RECOMMENDED STARTING AND MAINTENANCE DOSES

FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

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

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

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

Women: 0.85 x the value calculated for men.

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

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

INTRAVENOUS ADMINISTRATION

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

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

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

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

COMPATIBILITY AND STABILITY

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

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

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

HOW SUPPLIED

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

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

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

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

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

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

STORAGE

Vial: Store between 5-30°C (41-86°F).
Flexible Container: Store between 5-25°C (41-77°F).

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

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

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

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 intravenous doses as low as 5 mg/kg. After 6 months of intravenous dosing at 10 mg/kg/day, no nephropathological changes were noted; however, nephropathy was observed after dosing at 20 mg/kg/day for the same duration.

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

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

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

References:

1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically - Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January, 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests - Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.
3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Products Advisory Committee Meeting, March 31, 1993, Silver Spring MD.

Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA

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

5/2000

DESCRIPTION

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

[STRUCTURE]

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

[STRUCTURE]

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

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

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

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

CLINICAL PHARMACOLOGY

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

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

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

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

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

Parameters	500 mg q12h, P.O.	400 mg q12h, I.V.	750 mg q12h, P.O.	400 mg q8h, I.V.
AUC (μg●hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max}(μg/mL	2.97	4.56	3.59	4.07

[a]AUC_{0-12h} [b]$AUC_{24h}=AUC_{0-12h}x2$ [c]$AUC_{24h}=AUC_{0-8h}x3$

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250-mg oral dose, urine

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

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

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

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

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

Pharmacokinetic studies of the oral (single dose) and intravenous (single and multiple dose) forms of ciprofloxacin indicate that plasma concentrations of ciprofloxacin are higher in elderly subjects (>65 years) as compared to young

adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant. (See **PRECAUTIONS: Geriatric Use**.)

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

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

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

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

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

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

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin susceptible)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

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

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

Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (methicillin susceptible)
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic gram-negative microorganisms
Citrobacter diversus
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

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

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

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis

Aerobic gram-negative microorganisms

Acinetobacter lwoffi	*Pasteurella multocida*
Aeromonas hydrophila	*Salmonella enteritidis*
Edwardsiella tarda	*Vibrio cholerae*
Enterobacter aerogenes	*Vibrio parahaemolyticus*
Klebsiella oxytoca	*Vibrio vulnificus*
Legionella pneumophila	*Yersinia enterocolitica*

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

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

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

For testing aerobic microorganisms other than *Haemophilus influenzae*, *Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

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

[a]These interpretive standards are applicable only to broth microdilution susceptibility tests with streptococci using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae* [b]:

MIC (µg/mL)	**Interpretation**
≤ 1	Susceptible (S)

[b] This interpretive standard is applicable only to broth microdilution susceptibility tests with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using *Haemophilus* Test Medium[1].

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

For testing *Neisseria gonorrhoeae* [c]:

MIC (µg/mL)	**Interpretation**
≤ 0.06	Susceptible (S)

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

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

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

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

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

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

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

Diffusion Techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg ciprofloxacin to test the susceptibility of microorganisms to ciprofloxacin.

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

For testing aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae*, and *Neisseria gonorrhoeae*[a]:

Zone Diameter (mm)	**Interpretation**
≥21	Susceptible (S)
16-20	Intermediate (I)
≤15	Resistant (R)

[a] These zone diameter standards are applicable only to tests performed for streptococci using Mueller-Hinton agar supplemented with 5% sheep blood incubated in 5% CO_2.

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*[b]:

Zone Diameter(mm)	Interpretation
•21	Susceptible (S)

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

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

For testing *Neisseria gonorrhoeae* [c]:

Zone Diameter (mm)	Interpretation
≥36	Susceptible (S)

[c] This zone diameter standard is applicable only to disk diffusion tests with GC agar base and 1% defined growth supplement.

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

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

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

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

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

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

INDICATIONS AND USAGE

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CONTRAINDICATIONS

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

WARNINGS

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE), PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers** subsections.) The oral administration of ciprofloxacin caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints

and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY**.)

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

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

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

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in

patients who present with diarrhea subsequent to the administration of antibacterial agents.

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

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

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

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

PRECAUTIONS

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

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

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

Moderate to severe phototoxicity manifested as an exaggerated sunburn reaction has been observed in patients who are exposed to direct sunlight while receiving

some members of the quinolone class of drugs. Excessive sunlight should be avoided. Therapy should be discontinued if phototoxicity occurs.

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

Information for Patients:
Patients should be advised:

- that ciprofloxacin may be taken with or without meals and to drink fluids liberally. As with other quinolones, concurrent administration of ciprofloxacin with magnesium/aluminum antacids, or sucralfate, Videx® (didanosine) chewable/buffered tablets or pediatric powder, or with other products containing calcium, iron or zinc should be avoided. These products may be taken two hours after or six hours before ciprofloxacin. Ciprofloxacin should not be taken concurrently with milk or yogurt alone, since absorption of ciprofloxacin may be significantly reduced. Dietary calcium as part of a meal, however, does not significantly affect ciprofloxacin absorption

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

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

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

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

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

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

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

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

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

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

Histamine H_2-receptor antagonists appear to have no significant effect on the bioavailability of ciprofloxacin.

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

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

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

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

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

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

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

Salmonella/Microsome Test (Negative)

E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)

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

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

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

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

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

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

Pregnancy: Teratogenic Effects. Pregnancy Category C: Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally) produced

gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose. After intravenous administration of doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well-controlled studies in pregnant women. Ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See **WARNINGS**.)

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria,

urinary retention, urethral bleeding, vaginitis, acidosis
RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism
SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum (See above.) Allergic reactions ranging from urticaria to anaphylactic reactions have been reported. (See **WARNINGS**.)
SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste

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

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

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

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

Post-Marketing Adverse Events: Additional adverse events, regardless of relationship to drug, reported from worldwide marketing experience with quinolones, including ciprofloxacin, are:
BODY AS A WHOLE: change in serum phenytoin
CARDIOVASCULAR: postural hypotension, vasculitis
CENTRAL NERVOUS SYSTEM: agitation, confusion, delirium, dysphasia, myoclonus, nystagmus, toxic psychosis
GASTROINTESTINAL: constipation, dyspepsia, flatulence, hepatic necrosis, jaundice, pancreatitis, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment.)

HEMIC/LYMPHATIC: agranulocytosis, hemolytic anemia, methemoglobinemia, prolongation of prothrombin time
METABOLIC/NUTRITIONAL: elevation of serum triglycerides, cholesterol, blood glucose, serum potassium
MUSCULOSKELETAL: myalgia, possible exacerbation of myasthenia gravis, tendinitis/tendon rupture
RENAL/UROGENITAL: albuminuria, candiduria, renal calculi, vaginal candidiasis
SKIN/HYPERSENSITIVITY: anaphylactic reactions, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis
SPECIAL SENSES: anosmia, taste loss (See **PRECAUTIONS.**)

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

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

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

OVERDOSAGE

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

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

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

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

DOSAGE AND ADMINSTRATION

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

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

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

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

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

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

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

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

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

DOSAGE GUIDELINES				
Infection	**Type or Severity**	**Unit Dose**	**Frequency**	**Usual Durations†**
Acute Sinusitis	Mild/Moderate	500-mg	q 12 h	10 days
Lower Respiratory Tract	Mild/Moderate	500-mg	q 12 h	7 to 14 days
	Severe/Complicated	750-mg	q 12 h	7 to 14 days

Urinary Tract	Acute Uncomplicated	100-mg or 250-mg	q 12 h	3 Days
	Mild/Moderate	250-mg	q 12 h	7 to 14 Days
	Severe/Complicated	500-mg	q 12 h	7 to 14 Days
Chronic Bacterial Prostatitis	Mild/Moderate	500-mg	q 12 h	28 Days
Intra-Abdominal*	Complicated	500-mg	q 12 h	7 to 14 Days
Skin and Skin Structure	Mild/Moderate	500-mg	q 12 h	7 to 14 Days
	Severe/Complicated	750-mg	q 12 h	7 to 14 Days
Bone and Joint	Mild/Moderate	500-mg	q 12 h	≥ 4 to 6 weeks
	Severe/Complicated	750-mg	q 12 h	≥ 4 to 6 weeks
Infectious Diarrhea	Mild/Moderate/Severe	500-mg	q 12 h	5 to 7 Days
Typhoid Fever	Mild/Moderate	500-mg	q 12 h	10 Days
Urethral and Cervical Gonococcal Infections	Uncomplicated	250-mg	single dose	single dose

* used in conjunction with metronidazole
† Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared.

One teaspoonful (5 mL) of 5% ciprofloxacin oral suspension = 250-mg of ciprofloxacin.
One teaspoonful (5 mL) of 10% ciprofloxacin oral suspension = 500-mg of ciprofloxacin.
See Instructions for USE/HANDLING.

	Volume (mL) of Oral Suspension	
Dosage	5%	10%
250-mg	5 mL	2.5 mL
500-mg	10 mL	5 mL
750-mg	15 mL	7.5 mL

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

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

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

The duration of treatment depends upon the severity of infection. Generally ciprofloxacin should be continued for at least 2 days

after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for 4 to 6 weeks or longer. Chronic Bacterial Prostatitis should be treated for 28 days. Infectious diarrhea may be treated for 5-7 days. Typhoid fever should be treated for 10 days.

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

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

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

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

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

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

Women: 0.85 x the value calculated for men.
The serum creatinine should represent a steady state of renal function.

In patients with severe infections and severe renal impairment, a unit dose of 750-mg may be administered at the intervals noted above; however, patients should be carefully monitored and the serum ciprofloxacin concentration should

be measured periodically. Peak concentrations (1-2 hours after dosing) should generally range from 2 to 4 μg/mL.

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

HOW SUPPLIED

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

	Strength	**NDC Code**	**Tablet Identification**
Bottles of 50:	750-mg	NDC 0026-8514-50	CIPRO 750
Bottles of 100:	250-mg	NDC 0026-8512-51	CIPRO 250
	500-mg	NDC 0026-8513-51	CIPRO 500
Unit Dose			
Package of 100:	250-mg	NDC 0026-8512-48	CIPRO 250
	500-mg	NDC 0026-8513-48	CIPRO 500
	750-mg	NDC 0026-8514-48	CIPRO 750
Cystitis			
Package of 6:	100-mg	NDC 0026-8511-06	CIPRO 100

Store below 30°C (86°F).

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

Total volume after reconstitution	**Ciprofloxacin contents after reconstitution**	**Ciprofloxacin contents per bottle**	**NDC Code**

100 mL	250 mg/5 mL	5,000 mg	0026-8551-36
100 mL	500 mg/5 mL	10,000 mg	0026-8553-36

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

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

ANIMAL PHARMACOLOGY

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

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

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

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

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

CLINICAL STUDIES

Acute Sinusitis Studies

Ciprofloxacin tablets (500-mg BID) were evaluated for the treatment of acute sinusitis in two randomized, double-blind, controlled clinical trials conducted in the United States. Study 1 compared ciprofloxacin with cefuroxime axetil (250-mg BID) and enrolled 501 patients (400 of whom were valid for the primary

efficacy analysis). Study 2 compared ciprofloxacin with clarithromycin (500-mg BID) and enrolled 560 patients (418 of whom were valid for the primary efficacy analysis). The primary test of cure endpoint was a follow-up visit performed approximately 30 days after the completion of treatment with study medication. Clinical response data from these studies are summarized below:

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

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

Uncomplicated Cystitis Studies

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

	Clinical Response	Bacteriological Response By Organism (Eradication Rate)	
Drug Regimen	**Resolution n(%)**	***E. coli* n(%)**	***S. saprophyticus* n(%)**
	STUDY 1		
CIPRO 100-mg BID x 3 days	82/94 (87)	64/70 (91)	8/8 (100)
CIPRO 250-mg BID x 7 days	81/86 (94)	67/69 (97)	4/4 (100)
	STUDY 2		
CIPRO 100-mg BID x 3 days	134/141 (95)	117/123 (95)	8/8 (100)

Control (3 days)	128/133 (96)	103/105 (98)	10/10 (100)

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

Preparation of the suspension:

[IMAGE]	1. The small bottle contains the microcapsules; the large bottle contains the diluent.
[IMAGE]	2. Open both bottles. Child-proof cap: Press down according to instructions on the cap while turning to the left.
[IMAGE]	3. Pour the microcapsules completely into the large bottle of diluent. **Do not add water to the suspension.**
	4. Remove the top layer of the diluent bottle label (to reveal the CIPRO ® Oral Suspension label).
[IMAGE]	5. Close the large bottle completely according to the directions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

Instructions To The Patient For Taking CIPRO ® Oral Suspension:

Shake vigorously each time before use for approximately 15 seconds.

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

References: 1. National Committee for Clinical Laboratory Standards, Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically-

Fourth Edition. Approved Standard NCCLS Document M7-A4, Vol. 17, No. 2, NCCLS, Wayne, PA, January 1997.
2. National Committee for Clinical Laboratory Standards, Performance Standards for Antimicrobial Disk Susceptibility Tests-Sixth Edition. Approved Standard NCCLS Document M2-A6, Vol. 17, No. 1, NCCLS, Wayne, PA, January, 1997.
3. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Product's Advisory Committee meeting, March 31, 1993, Silver Spring MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA

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