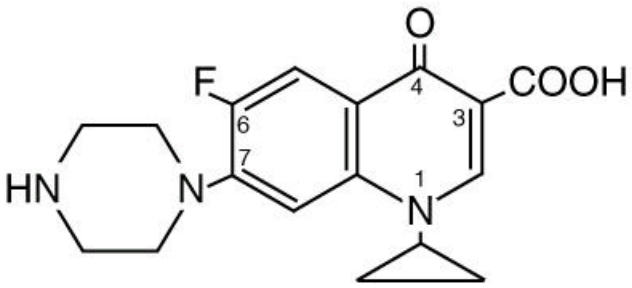
CIPRO® I.V.
(ciprofloxacin)
For Intravenous Infusion

PZXXXXXX **2/02**

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 is a faint to light yellow crystalline powder with a molecular weight of 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol. CIPRO I.V. solutions are available as sterile 1.0% aqueous concentrates, which are intended for dilution prior to administration, and as 0.2% ready-for-use infusion solutions in 5% Dextrose Injection. All formulas contain lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1% aqueous concentrates in vials is 3.3 to 3.9. The pH range for the 0.2% ready-for-use infusion solutions is 3.5 to 4.6.

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

CLINICAL PHARMACOLOGY

Absorption

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

Steady-state Ciprofloxacin Serum Concentrations (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. 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 Cmax 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

Distribution

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

Metabolism

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

Excretion

The serum elimination half-life is approximately 5-6 hours and the total clearance is around 35 L/hr. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg I.V. dose, concentrations in the urine usually exceed 200 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.

Special Populations

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

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

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

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

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

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

Aerobic gram-positive microorganisms

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

Aerobic gram-negative microorganisms

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

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

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

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

Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-resistant strains)

Aerobic gram-negative microorganisms

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

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

Susceptibility Tests

Dilution Techniques: Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method[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*, and *Haemophilus parainfluenzae*[a]:

MIC (mg/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 (mg/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.

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
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].

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,* and *Haemophilus parainfluenzae* [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.

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
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].

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.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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.

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), - EXCEPT FOR USE IN INHALATIONAL ANTHRAX (POST-EXPOSURE), PREGNANT WOMEN, AND LACTATING WOMEN HAVEN 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 ADMINISTRATION**.)

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.
- that ciprofloxacin may cause dizziness and lightheadedness.
- that ciprofloxacin may increase the effects of theophylline and caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking ciprofloxacin.
- to discontinue treatment; rest and refrain from exercise; and inform their physician if they experience pain, inflammation, or rupture of a tendon.
- that convulsions have been reported in patients taking quinolones, including ciprofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

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

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

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

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

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

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

Quinolones 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.

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 ½hour and 1.18 μg/mL between 6-8 hours after the end of infusion.

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

Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{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: There are no adequate and well-controlled studies in pregnant women. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS – the Teratogen Information System - concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data=fair), but the data are insufficient to state that there is no risk.[7]

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

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

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

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

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

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

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

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

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

Local I.V. site reactions 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

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time

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, myasthenia gravis

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

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:
change in serum phenytoin, postural hypotension, vasculitis, agitation, delirium, myoclonus, toxic psychosis, hemolytic anemia, methemoglobinemia, elevation of serum triglycerides, cholesterol, blood glucose, and serum potassium, myalgia, tedinitis/tendon rupture, 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 creatine phosphokinase, serum theophylline (in patients receiving theophylline concomitantly), blood glucose, and triglycerides.

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

OVERDOSAGE

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

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

DOSAGE AND ADMINISTRATION

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

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

DOSAGE GUIDELINES

Intravenous

Infection†	Type or Severity	Unit Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q12h	7-14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10-14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7-14 Days
	Severe/Complicated	400 mg	q8h	7-14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4-6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4-6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7-14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin	400 mg 50 mg/kg Not to exceed 24 g/day	q8h q4h	7-14 Days
Inhalational anthrax (post-exposure) **	Adult	400 mg	q12h	60 Days
	Pediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q12h	60 Days

* used in conjunction with metronidazole. (See product labeling for prescribing information.)

†DUE TO THE DESIGNATED PATHOGENS (See **INDICATIONS AND USAGE**.)

** Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum

concentrations achieved in humans, reasonably likely to predict clinical benefit.[4] For a discussion of ciprofloxacin serum concentrations in various human populations, see **INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION.** Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

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

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

Equivalent AUC Dosing Regimens

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

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

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.

Preparation of CIPRO I.V. for Administration

Vials (Injection Concentrate): THIS PREPARATION MUST BE DILUTED BEFORE USE. The intravenous dose should be prepared by aseptically withdrawing the

concentrate from the vial of CIPRO I.V. This should be diluted with a suitable intravenous solution to a final concentration of 1-2mg/mL. (See **COMPATIBILITY AND STABILITY.**) The resulting solution should be infused over a period of 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place.

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

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

COMPATIBILITY AND STABILITY

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

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

HOW SUPPLIED

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

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

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

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

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

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

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

STORAGE

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

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

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

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

* Does not comply with USP.

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.

INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION

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

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

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