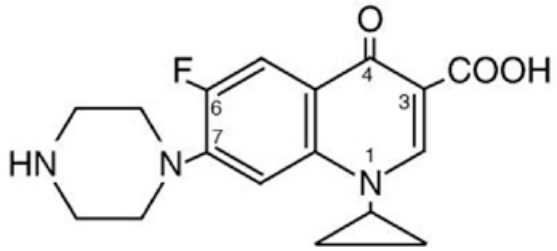
CIPROFLOXACIN - ciprofloxacin injection, solution, concentrate
Hospira, Inc.

Injection, USP
For Intravenous Infusion
Rx only

WARNING:
Fluoroquinolones, including ciprofloxacin are associated with an increased risk of tendonitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See WARNINGS).
Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis (See WARNINGS).

To reduce the development of drug-resistant bacteria and maintain the effectiveness of ciprofloxacin and other antibacterial drugs, Ciprofloxacin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

DESCRIPTION
Ciprofloxacin Injection, USP is a synthetic broad-spectrum antimicrobial agent for intravenous (IV) 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. Ciprofloxacin Injection, USP is available as a sterile 1% aqueous concentrate, which is intended for dilution prior to administration. The formula contains lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1% aqueous concentrate in vials is 3.3 to 3.9.

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 mcg/mL, respectively; the concentrations at 12 hours were 0.1 and 0.2 mcg/mL, respectively.

Steady-state Ciprofloxacin Serum Concentrations (mcg/mL) After 60-minute IV 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 IV 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 to 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 IV 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 IV Doses				
Parameters	**500 mg**	**400 mg**	**750 mg**	**400 mg**
	q12h, P.O.	q12h, IV	q12h, P.O.	q8h, IV
AUC (mcg•hr/mL)	13.7[a]	12.7[a]	31.6[b]	32.9[c]
C_{max} (mcg/mL)	2.97	4.56	3.59	4.07

[a] AUC_{0-12h}
[b] AUC 24h = AUC_{0-12h} x 2
[c] AUC 24h = AUC_{0-8h} x 3

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 IV 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%.
Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the coadministered drug (see **CONTRAINDICATIONS**, **WARNINGS**, and **PRECAUTIONS: Drug Interactions**).

Excretion
The serum elimination half-life is approximately 5 to 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 IV dose, concentrations in the urine usually exceed 200 mcg/mL 0 to 2 hours after dosing and are generally greater than 15 mcg/mL 8 to 12 hours after dosing. Following a 400 mg IV dose, urine concentrations generally exceed 400 mcg/mL 0 to 2 hours after dosing and are usually greater than 30 mcg/mL 8 to 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.
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 IV dose is recovered from the feces within 5 days 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 to 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**.)

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

Hepatic Impairment
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.

Pediatrics
Following a single oral dose of 10 mg/kg ciprofloxacin suspension to 16 children ranging in age from 4 months to 7 years, the mean C_{max} was 2.4 mcg/mL (range: 1.5 to 3.4 mcg/mL) and the mean AUC was 9.2 mcg*h/mL (range: 5.8 to 14.9 mcg*h/mL). There was

no apparent age-dependence, and no notable increase in C_{max} or AUC upon multiple dosing (10 mg/kg TID). In children with severe sepsis who were given intravenous ciprofloxacin (10 mg/kg as a 1-hour infusion), the mean C_{max} was 6.1 mcg/mL (range: 4.6 to 8.3 mcg/mL) in 10 children less than 1 year of age; and 7.2 mcg/mL (range: 4.7 to 11.8 mcg/mL) in 10 children between 1 and 5 years of age. The AUC values were 17.4 mcg*h/mL (range: 11.8 to 32 mcg*h/mL) and 16.5 mcg*h/mL (range: 11 to 23.8 mcg*h/mL) in the respective age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of pediatric patients with various infections, the predicted mean half-life in children is approximately 4 to 5 hours, and the bioavailability of the oral suspension is approximately 60%.

Drug-drug Interactions

Concomitant administration with tizanidine is contraindicated. (See **CONTRAINDICATIONS**.) 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 **WARNINGS** and **PRECAUTIONS**: **Drug Interactions**.)

Microbiology

Mechanism of Action

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.

Mechanism of Resistance

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 Resistance to fluoroquinolones occurs primarily by either mutation in the DNA gyrases, decreased outer membrane permeability, or drug efflux. *In vitro* resistance to ciprofloxacin develops slowly by multiple step mutations. Resistance to ciprofloxacin due to spontaneous mutation occurs at a general frequency of between $<10^{-9}$ to $1x10^{-6}$.

Cross Resistance

There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials.

Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as described in the **INDICATIONS AND USAGE** section of the package insert for ciprofloxacin injection.

Gram-positive bacteria

Enterococcus faecalis
Staphylococcus aureus
Staphylococcus epidermidis
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-negative bacteria

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

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.** At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentrations (MIC) less than or equal to the susceptible breakpoint for ciprofloxacin (≤mcg/mL). However, the efficacy of ciprofloxacin in treating clinical infections due to these bacteria **has not been** established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Staphylococcus haemolyticus
Staphylococcus hominis

Gram-negative bacteria

Acinetobacter Iwoffi	*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*
Pasteurella multocida	*Vibrio vulnificus*

Salmonella enteritidis *Yersinia enterocolitica*

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide the results of *in vitro* susceptibility test results for antimicrobial drug products used in resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

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 test method (broth and/or agar).[1] The MIC values should be interpreted according to criteria provided in Table 1.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters can also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. The zone size provides an estimate of the susceptibility of bacteria to antimicrobial compounds. The zone size should be determined using a standardized test method.[2] This procedure uses paper disks impregnated with 5 mcg ciprofloxacin to test the susceptibility of bacteria to ciprofloxacin. The disc diffusion interpretive criteria are provided in Table 1.

Table 1: Susceptibility Test Interpretive Criteria for Ciprofloxacin

	MIC (mcg/mL)			**Zone Diameter (mm)**		
Species	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤1	2	≥4	≥21	16-20	≤15
Enterococcus faecalis	≤1	2	≥4	≥21	16-20	≤15
Staphylococcus species	≤1	2	≥4	≥21	16-20	≤15
Pseudomonas aeruginosa	≤1	2	≥4	≥21	16-20	≤15
Haemophilus influenzae[a]	≤1			≥21		
Haemophilus parainfluenzae[a]	≤1			≥21		
Streptococcus pneumoniae	≤1	2	≥4	≥21	16-20	≤15
Streptococcus pyogenes	≤1	2	≥4	≥21	16-20	≤15

S = Susceptible, I = Intermediate, and R = Resistant.

[a] The current absence of data on resistant strains precludes defining any results other than “Susceptible.” Strains yielding zone diameter results suggestive of a “Non-Susceptible” 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.

Quality Control
Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.[1,2] For dilution technique, standard ciprofloxacin powder should provide the MIC values according to criteria outlined in Table 2.:
Table 2: Quality Control for Susceptibility Testing of Ciprofloxacin

Strains	**MIC range (mcg/mL)**	**Zone Diameter (mm)**
Enterococcus faecalis ATCC 29212	0.25-2	-
Escherichia coli ATCC 25922	0.004-0.015	30-40
Haemophilus influenzae ATCC 49247	0.004-0.03	34-42
Pseudomonas aeruginosa ATCC 27853	0.25-1	25-33
Staphylococcus aureus ATCC 29213	0.12-0.5	-
Staphylococcus aureus ATCC 25923	-	22-30

INDICATIONS AND USAGE
Ciprofloxacin Injection, USP is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below when the intravenous administration offers a route of administration advantageous to the patient. Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.
Adult Patients:
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*, methicillin-susceptible *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 penicillin-susceptible *Streptococcus pneumoniae*. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.
*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*, methicillin-susceptible *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*, penicillin-susceptible *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**.)
Pediatric Patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis due to *Escherichia coli*.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. (See **WARNINGS, PRECAUTIONS: Pediatric Use**, **ADVERSE REACTIONS,** and **CLINICAL STUDIES.**) Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals. (See **ANIMAL PHARMACOLOGY.**)
Adult and Pediatric Patients:
Inhalational Anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.
Ciprofloxacin serum concentrations achieved in humans served as a surrogate endpoint reasonably likely to predict clinical benefit and provided the initial basis for approval of this indication.[4] Supportive clinical information for ciprofloxacin for anthrax post-

exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001. (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 Ciprofloxacin Injection, USP 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.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ciprofloxacin Injection, USP and other antibacterial drugs, Ciprofloxacin Injection, USP should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components. (See **DESCRIPTION**.)

Concomitant administration with tizanidine is contraindicated. (See **PRECAUTIONS: Drug Interactions**.)

WARNINGS

Tendinopathy and Tendon Rupture

Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS: Post-Marketing Adverse Event Reports**.)

Pregnant Women

THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pregnancy** and **Nursing Mothers** subsections.)

Hypersensitivity Reactions

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.

Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (for example, toxic epidermal necrolysis, Stevens-Johnson syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;

- hepatitis; jaundice; acute hepatic necrosis or failure;

- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.**)

Theophylline

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.

Central Nervous System Effects

Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving fluoroquinolones, 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 fluoroquinolones, 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**.**)**

***Clostridium Difficile*-Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Peripheral neuropathy

Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness, or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation, and/or motor strength in order to prevent the development of an irreversible condition.

Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Ciprofloxacin should be used in pediatric patients (less than 18 years of age) only for infections listed in the **INDICATIONS AND USAGE** section. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS**.)

In pre-clinical studies, 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**.)

Prolongation of the QT Interval

Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during post-marketing surveillance in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval. (See **PRECAUTIONS, Drug Interactions** and **Geriatric Use**.)

Cytochrome P450 (CYP450)

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the coadministered drug and could lead to clinically significant pharmacodynamic side effects of the coadministered drug. (See **PRECAUTIONS, Drug Interactions**.)

PRECAUTIONS

General

INTRAVENOUS CIPROFLOXACIN SHOULD BE ADMINISTERED BY SLOW INFUSION OVER A PERIOD OF 60 MINUTES. Local IV 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**.)

Central Nervous System

Quinolones, including ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia. (See **PRECAUTIONS: 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.

Renal Impairment

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

Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (for example, burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs. (See **ADVERSE REACTIONS: Post-Marketing Adverse Event Reports.**)

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

Prescribing Ciprofloxacin Injection, USP in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Patients should be advised:

- to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue ciprofloxacin treatment. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

- that fluoroquinolones like ciprofloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Patients should call their healthcare provider right away if they have any worsening muscle weakness or breathing problems.

- that antibacterial drugs including Ciprofloxacin Injection, USP should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Ciprofloxacin Injection, USP is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by Ciprofloxacin Injection, USP or other antibacterial drugs in the future.

- 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 photosensitivity/phototoxicity has been reported in patients receiving quinolones. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking quinolones. If patients need to be outdoors while using quinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients should contact their physician.

- 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 increases the effects of tizanidine (Zanaflex®). Patients should not use ciprofloxacin if they are already taking tizanidine.

- 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.

- that peripheral neuropathies have been associated with ciprofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, they should discontinue treatment and contact their physicians.

- 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.

- that ciprofloxacin has been associated with an increased rate of adverse events involving joints and surrounding tissue structures (like tendons) in pediatric patients (less than 18 years of age). Parents should inform their child's physician if the child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy. (See **WARNINGS** and **PRECAUTIONS: Pediatric Use** and **ADVERSE REACTIONS**.)

- that diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions:

Tizanidine

In a pharmacokinetic study, systemic exposure of tizanidine (4 mg single dose) was significantly increased (C_{max} 7-fold, AUC 10-fold) when the drug was given concomitantly with ciprofloxacin (500 mg bid for 3 days). The hypotensive and sedative effects of tizanidine were also potentiated. Concomitant administration of tizanidine and ciprofloxacin is contraindicated.

Theophylline

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.

Other Xanthine Derivatives

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. On concurrent administration of ciprofloxacin and caffeine or pentoxifylline containing products, elevated serum concentrations of these xanthine derivatives were reported.

Cyclosporine

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

Phenytoin

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

Glyburide

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

Metronidazole

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

Oral Anti-Coagulant

Simultaneous administration of ciprofloxacin with an oral anticoagulant may augment the effect of the anticoagulant. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. Prothrombin time and INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant (for example, warfarin).

Probenecid

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.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Duloxetine

In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in a 5-fold increase of in mean AUC and a 2.5-fold increase in mean Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

NSAIDs

Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

Ropinirole

In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with 500 mg ciprofloxacin twice-daily, the mean Cmax and mean AUC of ropinirole were increased by 60% and 84%, respectively. Monitoring for ropinirole-related side effects and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin. (See **WARNINGS, Cytochrome P450 (CYP450)**.)

Lidocaine

In a study conducted in 9 healthy volunteers, concomitant use of 1.5 mg/kg IV lidocaine with 500 mg ciprofloxacin twice daily, resulted in an increase of lidocaine Cmax and AUC by 12% and 26%, respectively. Although lidocaine treatment was well tolerated at this elevated exposure, a possible interaction with ciprofloxacin and an increase in side effects related to lidocaine may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with 304 mg clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Careful monitoring of clozapine associated adverse effects and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised. (See **WARNINGS.**)

Sildenafil

Following concomitant administration of a single oral dose of 50 mg sildenafil with 500 mg ciprofloxacin to healthy subjects, the mean Cmax and mean AUC of sildenafil were both increased approximately two-fold. Therefore, sildenafil should be used with caution when co-administered with ciprofloxacin.

Class IA or III Antiarrhythmics

Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics as ciprofloxacin may have an additive effect on the QT interval (see **PRECAUTIONS**, **Geriatric Use**).

Piperacillin Sodium

Following infusion of 400 mg IV ciprofloxacin every eight hours in combination with 50 mg/kg IV piperacillin sodium every four hours, mean serum ciprofloxacin concentrations were 3.02 mcg/mL 0.5 hour and 1.18 mcg/mL between 6 to 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 rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 and 750 mg/kg to rats and mice, respectively (approximately 1.7 and 2.5 times the highest recommended therapeutic dose based upon mg/m^2).

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 to 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 (approximately 0.7 times the highest recommended therapeutic dose based upon mg/m^2) 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 to 5%). Rates of spontaneous abortions, prematurity and low birth weight did not differ between the groups and there were no clinically significant musculoskeletal 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 post-marketing 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, oral ciprofloxacin dose levels of 30 and 100 mg/kg (approximately 0.4 times and 1.3 times the highest recommended therapeutic dose based upon mg/m^2) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3 times the highest recommended therapeutic dose based upon mg/m^2) no maternal toxicity was produced, 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 risk of serious adverse reactions (including articular damage) 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

Ciprofloxacin, like other quinolones, causes arthropathy and histological changes in weight-bearing joints of juvenile animals resulting in lameness. (See **ANIMAL PHARMACOLOGY**.)

Inhalational Anthrax (Post-Exposure)

Ciprofloxacin is indicated in pediatric patients for 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**.

Complicated Urinary Tract Infection and Pyelonephritis

Ciprofloxacin is indicated for the treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli.* Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to the controls, including those related to joints and/or surrounding tissues. The rates of these events in pediatric patients with complicated urinary tract infection and pyelonephritis within six weeks of follow-up were 9.3% (31/335) versus 6.0% (21/349) for control agents. The rates of these events occurring at any time up to the one year follow-up were 13.7% (46/335) and 9.5% (33/349), respectively. The rate of all adverse events regardless of drug relationship at six weeks was 41% (138/335) in the ciprofloxacin arm compared to 31% (109/349) in the control arm. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES.**)

Cystic Fibrosis

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 to 17 years), 67 patients received ciprofloxacin IV 10 mg/kg/dose q8h for one week followed by ciprofloxacin tablets 20 mg/kg/dose q12h to complete 10 to 21 days treatment and 62 patients received the combination of ceftazidime IV 50 mg/kg/dose q8h and tobramycin IV 3 mg/kg/dose q8h for a total of 10 to 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 to 93 days). This study was not designed to determine long-term effects and the safety of repeated exposure to ciprofloxacin.

Musculoskeletal adverse events in patients with cystic fibrosis 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. Other adverse events were similar in nature and frequency between treatment arms. 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 cannot be definitively determined, particularly since patients with cystic fibrosis may develop arthralgias/arthritis as part of their underlying disease process.

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as ciprofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing ciprofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue ciprofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur (see **Boxed Warning**, **WARNINGS**, and **ADVERSE REACTIONS: Post-Marketing Adverse Event Reports**).

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**.)

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation of the QT interval (for example, class IA or class III antiarrhythmics) or in patients with risk factors for torsade de pointes (for example, known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

Adverse Reactions in Adult Patients

During clinical investigations with oral and parenteral ciprofloxacin, 49,038 patients received courses of the drug. 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. Ciprofloxacin was discontinued because of an adverse event in 1.8% of intravenously treated patients.

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy were nausea (2.5%), diarrhea (1.6%), liver function tests abnormal (1.3%), vomiting (1.0%), and rash (1.0%).

In clinical trials the following events were reported, regardless of drug relationship, in greater than 1% of patients treated with intravenous ciprofloxacin: nausea, diarrhea, central nervous system disturbance, local IV site reactions, liver function tests abnormal, eosinophilia, headache, restlessness, and rash. 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 IV site 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 medically important events, without regard to drug relationship or route of administration, that occurred in 1% or less of ciprofloxacin patients are listed below:

BODY AS A WHOLE: abdominal pain/discomfort, foot pain, pain, pain in extremities

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine

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, abnormal gait, grand mal convulsion, anorexia

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

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

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

RENAL/UROGENITAL: renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported.
RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, laryngeal or pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, bronchospasm
SKIN/HYPERSENSITIVITY: allergic reactions, anaphylactic reactions including life-threatening anaphylactic shock, 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, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity/phototoxicity reaction. (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, chromatopsia, 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 (IV and IV/P.O. sequential) with intravenous beta-lactam control antibiotics, the CNS adverse event profile of ciprofloxacin was comparable to that of the control drugs.

Adverse Reactions in Pediatric Patients

Ciprofloxacin, administered IV and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) or pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety within 6 weeks of therapy and through one year of follow-up in the 335 ciprofloxacin- and 349 comparator-treated patients enrolled.
An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse events as well as all patients with an abnormal gait or abnormal joint exam (baseline or treatment-emergent). These events were evaluated in a comprehensive fashion and included such conditions as arthralgia, abnormal gait, abnormal joint exam, joint sprains, leg pain, back pain, arthrosis, bone pain, pain, myalgia, arm pain, and decreased range of motion in a joint. The affected joints included: knee, elbow, ankle, hip, wrist, and shoulder. Within 6 weeks of treatment initiation, the rates of these events were 9.3% (31/335) in the ciprofloxacin-treated group versus 6.0% (21/349) in comparator-treated patients. The majority of these events were mild or moderate in intensity. All musculoskeletal events occurring by 6 weeks resolved (clinical resolution of signs and symptoms) usually within 30 days of end of treatment. Radiological evaluations were not routinely used to confirm resolution of the events. The events occurred more frequently in ciprofloxacin-treated patients than control patients, regardless of whether they received IV or oral therapy. Ciprofloxacin-treated patients were more likely to report more than one event and on more than one occasion compared to control patients. These events occurred in all age groups and the rates were consistently higher in the ciprofloxacin group compared to the control group. At the end of 1 year, the rate of these events reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) comparator-treated patients.
An adolescent female discontinued ciprofloxacin for wrist pain that developed during treatment. An MRI performed 4 weeks later showed a tear in the right ulnar fibrocartilage. A diagnosis of overuse syndrome secondary to sports activity was made, but a contribution from ciprofloxacin cannot be excluded. The patient recovered by 4 months without surgical intervention.
Findings Involving Joint or Peri-articular Tissues as Assessed by the IPSC

	Ciprofloxacin	**Comparator**
All Patients (within 6 weeks)	31/335 (9.3%)	21/349 (6%)
95% Confidence Interval*	(-0.8%, +7.2%)	
Age Group		
≥12 months <24 months	1/36 (2.8%)	0/41
≥2 years <6 years	5/124 (4.0%)	3/118 (2.5%)
≥6 years <12 years	18/143 (12.6%)	12/153 (7.8%)
≥12 years to 17 years	7/32 (21.9%)	6/37 (16.2%)

All Patients (within 1 year)	46/335 (13.7%)	33/349 (9.5%)
95% Confidence Interval*	(-0.6%, +9.1%)	

***** The study was designed to demonstrate that the arthropathy rate for the ciprofloxacin group did not exceed that of the control group by more than +6%. At both the 6 week and 1 year evaluations, the 95% confidence interval indicated that it could not be concluded that the ciprofloxacin group had findings comparable to the control group.

The incidence rates of neurological events within 6 weeks of treatment initiation were 3% (9/335) in the ciprofloxacin group versus 2% (7/349) in the comparator group and included dizziness, nervousness, insomnia, and somnolence.
In this trial, the overall incidence rates of adverse events regardless of relationship to study drug and within 6 weeks of treatment initiation were 41% (138/335) in the ciprofloxacin group versus 31% (109/349) in the comparator group. The most frequent events were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients.
Serious adverse events were seen in 7.5% (25/335) of ciprofloxacin-treated patients compared to 5.7% (20/349) of control patients. Discontinuation of drug due to an adverse event was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse events that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, accidental injury 3.0%, rhinitis 3.0%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.
In addition to the events reported in pediatric patients in clinical trials, it should be expected that events reported in adults during clinical trials or post-marketing experience may also occur in pediatric patients.

Post-Marketing Adverse Event Reports

The following adverse events have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these events in labeling are typically based on one or more of the following factors: (1) seriousness of the event, (2) frequency of the reporting, or (3) strength of causal connection to the drug.
Agitation, agranulocytosis, albuminuria, anosmia, candiduria, cholesterol elevation (serum), confusion, constipation, delirium, dyspepsia, dysphagia, erythema multiforme, exfoliative dermatitis, fixed eruption, flatulence, glucose elevation (blood), hemolytic anemia, hepatic failure (including fatal cases), hepatic necrosis, hyperesthesia, hypertonia, hypesthesia, hypotension (postural), jaundice, marrow depression (life threatening), methemoglobinemia, moniliasis (oral, gastrointestinal, vaginal), myalgia, myasthenia, exacerbation of myasthenia gravis, myoclonus, nystagmus, pancreatitis, pancytopenia (life threatening or fatal outcome), peripheral neuropathy, phenytoin alteration (serum), photosensitivity/phototoxicity reaction, polyneuropathy, potassium elevation (serum), prothrombin time prolongation or decrease, pseudomembranous colitis (The onset of pseudomembranous colitis symptoms may occur during or after antimicrobial treatment), psychosis (toxic), QT prolongation, renal calculi, serum sickness like reaction, Stevens-Johnson syndrome, taste loss, tendinitis, tendon rupture, torsade de pointes, toxic epidermal necrolysis (Lyell's Syndrome), triglyceride elevation (serum), twitching, vaginal candidiasis, and vasculitis, and ventricular arrhythmia. (See **PRECAUTIONS**.)
Adverse events were also reported by persons who received ciprofloxacin for anthrax post-exposure prophylaxis following the anthrax bioterror attacks of October 2001. (See also **INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION.**)

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 (γ 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, including monitoring of renal function. 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 - ADULTS

Ciprofloxacin Injection, USP should be administered to adults 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 Ciprofloxacin Injection, USP for Administration**.)

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.

ADULT DOSAGE GUIDELINES

Infection†	**Severity**	**Dose**	**Frequency**	**Usual Duration**
Urinary Tract	Mild/Moderate Severe/Complicated	200 mg 400 mg	q12h q12h (or q8h)	7 to 14 Days 7 to 14 Days
Lower Respiratory Tract	Mild/Moderate Severe/Complicated	400 mg 400 mg	q12h q8h	7 to 14 Days 7 to 14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10 to 14 Days
Skin and Skin Structure	Mild/Moderate Severe/Complicated	400 mg 400 mg	q12h q8h	7 to 14 Days 7 to 14 Days
Bone and Joint	Mild/Moderate Severe/Complicated	400 mg 400 mg	q12h q8h	≥4 to 6 Weeks ≥4 to 6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7 to 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 to 14 Days
Inhalational anthrax (post-exposure) **		400 mg	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.

Ciprofloxacin Injection, USP should be administered by intravenous infusion over a period of 60 minutes.

Conversion of IV to Oral Dosing in Adults

Parenteral therapy may be switched to oral ciprofloxacin 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	
Ciprofloxacin Oral Dosage	**Equivalent Ciprofloxacin Injection, USP Dosage**
250 mg Tablet q 12 h	200 mg IV q 12 h
500 mg Tablet q 12 h	400 mg IV q 12 h
750 mg Tablet q 12 h	400 mg IV q 8 h

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

Adults with 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 alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

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

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

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, careful monitoring is suggested.

Pediatrics

Ciprofloxacin Injection, USP should be administered as described in the Dosage Guidelines table. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed. (See **ADVERSE REACTIONS** and **CLINICAL STUDIES.**)

Dosing and initial route of therapy (i.e., IV or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6 to 10 mg/kg IV every 8 hours and allowed to switch to oral therapy (10 to 20 mg/kg every 12 hours), at the discretion of the physician.

	PEDIATRIC DOSAGE GUIDELINES

Infection	**Route of Administration**	**Dose (mg/kg)**	**Frequency**	**Total Duration**
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)	Intravenous	6 mg/kg to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing >51 kg)	Every 8 hours	10-21 days*
	Oral	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing >51 kg)	Every 12 hours	

Inhalational Anthrax (Post-Exposure)**	Intravenous	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
	Oral	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	

***** The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).
** Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores. 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.**

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of complicated urinary tract infection and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (i.e., creatinine clearance of <50 mL/min/1.73m^2).

Ciprofloxacin Injection, USP should be administered by intravenous infusion over a period of 60 minutes.

Preparation of Ciprofloxacin Injection, USP 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 Ciprofloxacin Injection, USP. This should be diluted with a suitable intravenous solution to a final concentration of 1 to 2 mg/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 Ciprofloxacin Injection, USP. If the concomitant use of Ciprofloxacin Injection, USP and another drug is necessary each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

COMPATIBILITY AND STABILITY

Ciprofloxacin Injection 1% (10 mg/mL), when diluted with the following intravenous solutions to concentrations of 0.5 to 2 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

Ciprofloxacin Injection, USP is available as a clear, colorless to slightly yellowish solution. Ciprofloxacin Injection, USP is available in 200 mg and 400 mg strengths. The concentrate is supplied in vials as follows:

Vial: manufactured by Hospira, Inc., Lake Forest, IL 60045 USA.

SIZE	STRENGTH	NDC NUMBER

20 mL	200 mg	0409-4765-86
40 mL	400 mg	0409-4778-86

Storage
Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.]
Protect from light, avoid excessive heat, protect from freezing.

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 young beagle dogs, oral ciprofloxacin doses of 30 mg/kg and 90 mg/kg ciprofloxacin (approximately 1.3- and 3.5-times the pediatric dose based upon comparative plasma AUCs), given daily for 2 weeks caused articular changes which were still observed by histopathology after a treatment-free period of 5 months. At 10 mg/kg (approximately 0.6-times the pediatric dose based upon comparative plasma AUCs), no effects on joints were observed. This dose was also not associated with arthrotoxicity after an additional treatment-free period of 5 months. In another study, 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 was noted after single oral doses as low as 5 mg/kg (approximately 0.07 times the highest recommended therapeutic dose based upon mg/m^2). 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 (approximately 0.2 times the highest recommended therapeutic dose based upon mg/m^2).
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 mcg/mL, and 4.56 mcg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady-state for both of these regimens is 0.2 mcg/mL. In a study of 10 pediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 mcg/mL and trough concentrations range from 0.09 to 0.26 mcg/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 mcg/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} (~5.5×10^5) spores (range 5 to 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 mcg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady-state ranged from 0.98 to 1.69 mcg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 mcg/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]
More than 9300 persons were recommended to complete a minimum of 60 days of antibiotic prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. Ciprofloxacin was recommended to most of those individuals for all or part of the prophylaxis regimen. Some persons were also given anthrax vaccine or were switched to alternative antibiotics. No one who received

ciprofloxacin or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received ciprofloxacin as all or part of their post-exposure prophylaxis regimen is unknown.
Among the persons surveyed by the Centers for Disease Control and Prevention, over 1000 reported receiving ciprofloxacin as sole post-exposure prophylaxis for inhalational anthrax. Gastrointestinal adverse events (nausea, vomiting, diarrhea, or stomach pain), neurological adverse events (problems sleeping, nightmares, headache, dizziness or lightheadedness) and musculoskeletal adverse events (muscle or tendon pain and joint swelling or pain) were more frequent than had been previously reported in controlled clinical trials. This higher incidence, in the absence of a control group, could be explained by a reporting bias, concurrent medical conditions, other concomitant medications, emotional stress or other confounding factors, and/or a longer treatment period with ciprofloxacin. Because of these factors and limitations in the data collection, it is difficult to evaluate whether the reported symptoms were drug-related.

CLINICAL STUDIES

EMPIRICAL THERAPY IN ADULT FEBRILE NEUTROPENIC PATIENTS

The safety and efficacy of ciprofloxacin, 400 mg IV q 8h, in combination with piperacillin sodium, 50 mg/kg IV 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 IV q 8h, in combination with piperacillin sodium, 50 mg/kg IV 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.

Complicated Urinary Tract Infection and Pyelonephritis - Efficacy in Pediatric Patients

NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.
Ciprofloxacin, administered IV and/or orally, was compared to a cephalosporin for treatment of complicated urinary tract infections (cUTI) and pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years). The trial was conducted in the US, Canada, Argentina, Peru, Costa Rica, Mexico, South Africa, and Germany. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). The primary objective of the study was to assess musculoskeletal and neurological safety. Patients were evaluated for clinical success and bacteriological eradication of the baseline organism(s) with no new infection or superinfection at 5 to 9 days post-therapy (Test of Cure or TOC). The Per Protocol population had a causative organism(s) with protocol specified colony count(s) at baseline, no protocol violation, and no premature discontinuation or loss to follow-up (among other criteria).
The clinical success and bacteriologic eradication rates in the Per Protocol population were similar between ciprofloxacin and the comparator group as shown below.
Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)

	Ciprofloxacin	**Comparator**
Randomized Patients	337	352

Per Protocol Patients	211	231
Clinical Response at 5 to 9 Days Post-Treatment	95.7% (202/211)	92.6% (214/231)
	95% CI [-1.3%, 7.3%]	
Bacteriologic Eradication by Patient at 5 to 9 Days Post-Treatment*	84.4% (178/211)	78.3% (181/231)
	95% CI [-1.3%, 13.1%]	
Bacteriologic Eradication of the Baseline Pathogen at 5 to 9 Days Post-Treatment		
Escherichia coli	156/178 (88%)	161/179 (90%)
* Patients with baseline pathogen(s) eradicated and no new infections or superinfections/total number of patients. There were 5.5% (6/211) ciprofloxacin and 9.5% (22/231) comparator patients with superinfections or new infections.		

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Revised: 12/2011

EN-2980

Hospira, Inc., Lake Forest, IL 60045 USA

MEDICATION GUIDE
Ciprofloxacin Injection, USP and Ciprofloxacin in 5% Dextrose Injection, USP
For Intravenous Infusion

Read the Medication Guide that comes with ciprofloxacin before you start taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about ciprofloxacin?

Ciprofloxacin belongs to a class of antibiotics called fluoroquinolones. Ciprofloxacin can cause side effects that may be serious or even cause death. If you get any of the following serious side effects, get medical help right away. Talk with your healthcare provider about whether you should continue to take ciprofloxacin.

1. Tendon rupture or swelling of the tendon (tendinitis)

- **Tendon problems can happen in people of all ages who take ciprofloxacin.** Tendons are tough cords of tissue that connect muscles to bones. Symptoms of tendon problems include:
  - Pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.
- **The risk of getting tendon problems while you take ciprofloxacin is higher if you:**
  - are over 60 years of age
  - are taking steroids (corticosteroids)
  - have had a kidney, heart, or lung transplant.
- **Tendon problems can happen in people who do not have the above risk factors when they take ciprofloxacin. Other reasons that can increase your risk of tendon problems can include:**
  - physical activity or exercise
  - kidney failure
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA).
- **Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation.** Stop taking ciprofloxacin until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area. The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons.
- **Talk to your healthcare provider about the risk of tendon rupture with continued use of ciprofloxacin.** You may need a different antibiotic that is not a fluoroquinolone to treat your infection.
- **Tendon rupture can happen while you are taking or after you have finished taking ciprofloxacin.** Tendon ruptures have happened up to several months after patients have finished taking their fluoroquinolone.
- **Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:**
  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area
  - unable to move the affected area or bear weight.

2. Worsening of myasthenia gravis (a disease which causes muscle weakness). Fluoroquinolones like ciprofloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

- **See the section "What are the possible side effects of ciprofloxacin?" for more information about side effects.**

What is ciprofloxacin?

Ciprofloxacin is a fluoroquinolone antibiotic medicine used to treat certain infections caused by certain germs called bacteria.

Children less than 18 years of age have a higher chance of getting bone, joint, or tendon (musculoskeletal) problems such as pain or swelling while taking ciprofloxacin. Ciprofloxacin should not be used as the first choice of antibiotic medicine in children under 18 years of age.

Ciprofloxacin should not be used in children under 18 years old, except to treat specific serious infections, such as complicated urinary tract infections and to prevent anthrax disease after breathing the anthrax bacteria germ (inhalational exposure).

Sometimes infections are caused by viruses rather than by bacteria. Examples include viral infections in the sinuses and lungs, such as the common cold or flu. Antibiotics, including ciprofloxacin, do not kill viruses.

Call your healthcare provider if you think your condition is not getting better while you are taking ciprofloxacin.

Who should not take ciprofloxacin?

Do not take ciprofloxacin if you:

- have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or are allergic to any of the ingredients in ciprofloxacin. Ask your healthcare provider if you are not sure. See the list of ingredients in ciprofloxacin at the end of this Medication Guide.
- also take a medicine called tizanidine (Zanaflex®). Serious side effects from tizanidine are likely to happen.

What should I tell my healthcare provider before taking ciprofloxacin?

See "**What is the most important information I should know about ciprofloxacin?**"

Tell your healthcare provider about all your medical conditions, including if you:

- have tendon problems
- have a disease that causes muscle weakness (myasthenia gravis)
- have central nervous system problems (such as epilepsy)

- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”
- have a history of seizures
- have kidney problems. You may need a lower dose of ciprofloxacin if your kidneys do not work well.
- have rheumatoid arthritis (RA) or other history of joint problems
- have trouble swallowing pills
- are pregnant or planning to become pregnant. It is not known if ciprofloxacin will harm your unborn child.
- are breast-feeding or planning to breast-feed. Ciprofloxacin passes into breast milk. You and your healthcare provider should decide whether you will take ciprofloxacin or breast-feed.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal and dietary supplements. Ciprofloxacin and other medicines can affect each other causing side effects. Especially tell your healthcare provider if you take:

- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take ciprofloxacin or other fluoroquinolones may increase your risk of central nervous system effects and seizures. See “**What are the possible side effects of ciprofloxacin?**”
- a blood thinner (such as warfarin, Coumadin®, Jantoven®)
- tizanidine (Zanaflex®) You should not take ciprofloxacin if you are already taking tizanidine. See “**Who should not take ciprofloxacin?**”
- theophylline (such as Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)
- glyburide (Micronase®, Glynase®, Diabeta®, Glucovance®). See “**What are the possible side effects of ciprofloxacin?**”
- phenytoin (Fosphenytoin Sodium®, Cerebyx®, Dilantin-125®, Dilantin®, Extended Phenytoin Sodium®, Prompt Penytoin Sodium®, Phenytek®)
- products that contain caffeine
- a medicine to control your heart rate or rhythm (antiarrhythmics). See “**What are the possible side effects of ciprofloxacin?**”
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- a steroid medicine. Corticosteroids taken by mouth or by injection may increase the chance of tendon injury. See “**What is the most important information I should know about ciprofloxacin?**”
- methotrexate (Trexall®)
- Probenecid (Probalan®, Col-probenecid®)
- Metoclopromide (Reglan®, Reglan ODT®)
- ropinirole (Requip®)
- lidocaine (Xylocaine® intravenous infusion)
- clozapine (Clozaril®, Fazaclo® ODT®)
- pentoxifylline (Trental®)
- sildenafil (Viagra®, Revatio®)
- cyclosporine (Gengraf®, Neoral®, Sandimmune®, Sangcya®)
- omeprazole

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take ciprofloxacin?

- Ciprofloxacin is given to you by intravenous (IV) infusion into your vein, slowly, over 60 minutes, as prescribed by your healthcare provider.

If you have been prescribed ciprofloxacin after being exposed to anthrax:

- Ciprofloxacin has been approved to lessen the chance of getting anthrax disease or worsening of the disease after you are exposed to the anthrax bacteria germ.
- Side effects may happen while you are taking ciprofloxacin to prevent anthrax infection, you and your healthcare provider should talk about whether the risks of stopping ciprofloxacin too soon are more important than the risks of side effects with ciprofloxacin.
- If you are pregnant, or plan to become pregnant while taking ciprofloxacin, you and your healthcare provider should decide whether the benefits of taking ciprofloxacin for anthrax are more important than the risks.

What should I avoid while taking ciprofloxacin?

- Ciprofloxacin can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how ciprofloxacin affects you.

- Avoid sunlamps, tanning beds, and try to limit your time in the sun. Ciprofloxacin can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while taking ciprofloxacin, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of ciprofloxacin?

Ciprofloxacin can cause side effects that may be serious or even cause death. See "**What is the most important information I should know about ciprofloxacin?**"

Other serious side effects of ciprofloxacin include:

- **Theophylline**

You may have serious seizure and breathing problems when you take theophylline with ciprofloxacin. These problems may lead to death. Get emergency help right away if you have seizures or trouble breathing.

- **Central Nervous System Effects**

Seizures have been reported in people who take fluoroquinolone antibiotics including ciprofloxacin. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking ciprofloxacin will change your risk of having a seizure. Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of ciprofloxacin. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

- feel dizzy
- seizures
- hear voices, see things, or sense things that are not there (hallucinations)
- feel restless
- tremors
- feel anxious or nervous
- confusion
- depression
- trouble sleeping
- nightmares
- feel more suspicious (paranoia)
- suicidal thoughts or acts

- **Serious allergic reactions**

Allergic reactions, including death, can happen in people taking fluoroquinolones, including ciprofloxacin, even after only one dose. Stop taking ciprofloxacin and get emergency medical help right away if you get any of the following symptoms of a severe allergic reaction:

- hives
- trouble breathing or swallowing
- swelling of the lips, tongue, face
- throat tightness, hoarseness
- rapid heartbeat
- faint
- yellowing of the skin or eyes. Stop taking ciprofloxacin and tell your healthcare provider right away if you get yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to ciprofloxacin (a liver problem).

- **Skin rash**

Skin rash may happen in people taking ciprofloxacin, even after only one dose. Stop taking ciprofloxacin at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to ciprofloxacin.

- **Serious heart rhythm changes (QT prolongation and torsade de pointes)**

Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. Ciprofloxacin may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this event are higher in people:

- who are elderly
- with a family history of prolonged QT interval,
- with low blood potassium (hypokalemia),
- who take certain medicines to control heart rhythm (antiarrhythmics).

- **Intestine infection (Pseudomembranous colitis)**

Pseudomembranous colitis can happen with most antibiotics, including ciprofloxacin. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and possible nerve damage (Peripheral Neuropathy)**

Damage to the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including ciprofloxacin. Talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- pain
- burning
- tingling
- numbness
- weakness

Ciprofloxacin may need to be stopped to prevent permanent nerve damage.

- **Low blood sugar (hypoglycemia)**

People who take ciprofloxacin and other fluoroquinolone medicines with the oral anti-diabetes medicine glyburide (Micronase, Glynase, Diabeta, Glucovance) can get low blood sugar (hypoglycemia) which can sometimes be severe. Tell your healthcare provider if you get low blood sugar with ciprofloxacin. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity).**

See "**What should I avoid while taking ciprofloxacin?**"

- **Joint Problems**

Increased chance of problems with joints and tissues around joints in children under 18 years old. Tell your child's healthcare provider if your child has any joint problems during or after treatment with ciprofloxacin.

The most common side effects of ciprofloxacin include:

- nausea
- headache
- diarrhea
- vomiting
- vaginal yeast infection
- changes in liver function tests
- pain or discomfort in the abdomen
- headache

These are not all the possible side effects of ciprofloxacin. Tell your healthcare provider about any side effect that bothers you, or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1–800–FDA–1088.

General Information about ciprofloxacin

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ciprofloxacin for a condition for which it is not prescribed. Do not give ciprofloxacin to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about ciprofloxacin. If you would like more information about ciprofloxacin, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ciprofloxacin that is written for healthcare professionals. For more information go to www.hospira.com or call 1-800-615-0187.

What are the ingredients in ciprofloxacin?

- Active ingredient: ciprofloxacin
- Inactive ingredients: lactic acid as a solubilizing agent, hydrochloric acid for pH adjustment

Revised: 12/2011

EN-2980

Hospira, Inc., Lake Forest, IL 60045 USA

RL-1282

RL-1283

Revised: 02/2013

Distributed by: Hospira, Inc.