**---------- ADVERSE REACTIONS ----------**

The most common adverse reactions ≥1% were nausea, diarrhea, liver function tests abnormal, vomiting, and rash. (6)

**To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.**

**---------- DRUG INTERACTIONS ----------**

| Interacting Drug | Interaction |
|---|---|
| Theophylline | Serious and fatal reactions. Avoid concomitant use. Monitor serum level (7) |
| Warfarin | Anticoagulant effect enhanced. Monitor prothrombin time, INR, and bleeding (7) |
| Antidiabetic agents | Hypoglycemia including fatal outcomes have been reported. Monitor blood glucose (7) |
| Phenytoin | Monitor phenytoin level (7) |
| Methotrexate | Monitor for methotrexate toxicity (7) |
| Cyclosporine | May increase serum creatinine. Monitor serum creatinine (7) |
| Multivalent cation-containing products including antacids, metal cations or didanosine | Decreased CIPRO absorption. Take CIPRO 2 hours before or 6 hours after administration of multivalent cation containing drugs (7) |

**---------- USE IN SPECIFIC POPULATIONS ----------**

**Lactation:** Breastfeeding is not recommended during treatment, but a lactating woman may pump and discard breastmilk during treatment and an additional 2 days after the last dose. In patients treated for inhalational anthrax (post exposure), consider the risks and benefits of continuing breastfeeding. **(**8.2**)**

**See full prescribing information** for use in pediatric and geriatric patients (8.4, 8.5)

**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

**Revised: 3/2021**

**FULL PRESCRIBING INFORMATION: CONTENTS***



*Sections or subsections omitted from the full prescribing information are not listed

**FULL PRESCRIBING INFORMATION**

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS**

- **Fluoroquinolones, including CIPRO®, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together *[see Warnings and Precautions (5.1)]* including*:***
  - **Tendinitis and tendon rupture *[see Warnings and Precautions (5.2)]***
  - **Peripheral neuropathy *[see Warnings and Precautions (5.3)]***
  - **Central nervous system effects *[see Warnings and Precautions (5.4)]***
- **Discontinue CIPRO immediately and avoid the use of fluoroquinolones, including CIPRO, in patients who experience any of these serious adverse reactions *[see Warnings and Precautions (5.1)]*. Fluoroquinolones, including CIPRO, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIPRO in patients with known history of myasthenia gravis *[see Warnings and Precautions (5.5)]*.**
- **Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions *[see Warnings and Precautions (5.1–5.16)]*, reserve CIPRO for use in patients who have no alternative treatment options for the following indications:**
  - **Acute exacerbation of chronic bronchitis *[see Indications and Usage (1.10)]***
  - **Acute uncomplicated cystitis *[see Indications and Usage (1.11)]***
  - **Acute sinusitis *[see Indications and Usage (1.12)]***

# 1 INDICATIONS AND USAGE

## 1.1 Skin and Skin Structure Infections

CIPRO is indicated in adult patients for treatment of skin and skin structure infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *Staphylococcus aureus,* methicillin-susceptible *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

## 1.2 Bone and Joint Infections

CIPRO is indicated in adult patients for treatment of bone and joint infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

## 1.3 Complicated Intra-Abdominal Infections

CIPRO is indicated in adult patients for treatment of complicated intra-abdominal infections (used in combination with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

## 1.4 Infectious Diarrhea

CIPRO is indicated in adult patients for treatment of infectious diarrhea caused by *Escherichia coli* (enterotoxigenic isolates), *Campylobacter jejuni, Shigella boydii* [†]**,** *Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei*[†] when antibacterial therapy is indicated.

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

### 1.5 Typhoid Fever (Enteric Fever)

CIPRO is indicated in adult patients for treatment of typhoid fever (enteric fever**)** caused by *Salmonella typhi.* The efficacy of ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

### 1.6 Uncomplicated Cervical and Urethral Gonorrhea

CIPRO is indicated in adult patients for treatment of uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae [see Warnings and Precautions (5.17)].*

### 1.7 Inhalational Anthrax (Post-Exposure)

CIPRO is indicated in adults and pediatric patients from birth to 17 years of age for 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.[1] Supportive clinical information for ciprofloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001 *[see Clinical Studies (14.2)].*

### 1.8 Plague

CIPRO is indicated for treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis (Y. pestis)* and prophylaxis for plague in adults and pediatric patients from birth to 17 years of age. Efficacy studies of ciprofloxacin could not be conducted in humans with plague for feasibility reasons. Therefore this indication is based on an efficacy study conducted in animals only *[see Clinical Studies (14.3)].*

### 1.9 Chronic Bacterial Prostatitis

CIPRO is indicated in adult patients for treatment of chronic bacterial prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*

### 1.10 Lower Respiratory Tract Infections

CIPRO is indicated in adult patients for treatment of lower respiratory tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Streptococcus pneumoniae.*

CIPRO is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

CIPRO is indicated for the treatment of acute exacerbations of chronic bronchitis (AECB) caused by *Moraxella catarrhalis.*

Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions *[see Warnings and Precautions (5.1–5.16)]* and for some patients AECB is self-limiting, reserve CIPRO for treatment of AECB in patients who have no alternative treatment options.

### 1.11 Urinary Tract Infections

*Urinary Tract Infections in Adults*

CIPRO is indicated in adult patients for treatment of urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter koseri, Citrobacter freundii, Pseudomonas aeruginosa,* methicillin-susceptible *Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis*.

*Acute Uncomplicated Cystitis*

CIPRO is indicated in adult female patients for treatment of acute uncomplicated cystitis caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions *[see Warnings and Precautions (5.1–5.16)]* and for some patients acute uncomplicated cystitis is self-limiting, reserve CIPRO for treatment of acute uncomplicated cystitis in patients who have no alternative treatment options.

*Complicated Urinary Tract Infection and Pyelonephritis in Pediatric Patients*

CIPRO is indicated in pediatric patients aged one to 17 years of age for treatment of complicated urinary tract infections (cUTI) and pyelonephritis due to *Escherichia coli [see Use in Specific Populations (8.4)]*.

Although effective in clinical trials, CIPRO is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls, including reactions related to joints and/or surrounding tissues. CIPRO, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals *[see Warnings and Precautions (5.13), Adverse Reactions (6.1), Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*.

### 1.12 Acute Sinusitis

CIPRO is indicated in adult patients for treatment of acute sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae,* or *Moraxella catarrhalis.*

Because fluoroquinolones, including CIPRO, have been associated with serious adverse reactions *[see Warnings and Precautions (5.1-5.16)]* and for some patients acute sinusitis is self-limiting, reserve CIPRO for treatment of acute sinusitis in patients who have no alternative treatment options.

### 1.13 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRO and other antibacterial drugs, CIPRO 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.

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

As with other drugs, some isolates 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.

## 2 DOSAGE AND ADMINISTRATION

CIPRO Tablets and Oral Suspension should be administered orally as described in the appropriate Dosage Guidelines tables.

### 2.1 Dosage in Adults

The determination of dosage and duration 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. CIPRO Tablets or Oral Suspension may be administered to adult patients when clinically indicated at the discretion of the physician. Administer CIPRO for Oral Suspension using the co-packaged graduated spoon *[see Dosage and Administration (2.7)]*.

**Table 1: Adult Dosage Guidelines**

| Infection | Dose | Frequency | Usual Durations[1] |
|---|---|---|---|
| Skin and Skin Structure | 500–750 mg | every 12 hours | 7 to 14 days |
| Bone and Joint | 500–750 mg | every 12 hours | 4 to 8 weeks |
| Complicated Intra–Abdominal[2] | 500 mg | every 12 hours | 7 to 14 days |
| Infectious Diarrhea | 500 mg | every 12 hours | 5 to 7 days |
| Typhoid Fever | 500 mg | every 12 hours | 10 days |
| Uncomplicated Urethral and Cervical Gonococcal Infections | 250 mg | single dose | single dose |
| Inhalational anthrax (post-exposure)[3] | 500 mg | every 12 hours | 60 days |
| Plague[3] | 500–750 mg | every 12 hours | 14 days |
| Chronic Bacterial Prostatitis | 500 mg | every 12 hours | 28 days |
| Lower Respiratory Tract Infections | 500–750 mg | every 12 hours | 7 to 14 days |
| Urinary Tract Infections | 250–500 mg | every 12 hours | 7 to 14 days |
| Acute Uncomplicated Cystitis | 250 mg | every 12 hours | 3 days |
| Acute Sinusitis | 500 mg | every 12 hours | 10 days |

1. Generally ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).
2. Used in conjunction with metronidazole.
3. Begin drug administration as soon as possible after suspected or confirmed exposure.

*Conversion of IV to Oral Dosing in Adults*

Patients whose therapy is started with CIPRO IV may be switched to CIPRO Tablets or Oral Suspension when clinically indicated at the discretion of the physician (Table 2) *[see Clinical Pharmacology (12.3)]*.

**Table 2: Equivalent AUC Dosing Regimens**

| CIPRO Oral Dosage | Equivalent CIPRO IV Dosage |
|---|---|
| 250 mg Tablet every 12 hours | 200 mg intravenous every 12 hours |
| 500 mg Tablet every 12 hours | 400 mg intravenous every 12 hours |
| 750 mg Tablet every 12 hours | 400 mg intravenous every 8 hours |

## 2.2 Dosage in Pediatric Patients

Dosing and initial route of therapy (that is, IV or oral) for cUTI or pyelonephritis should be determined by the severity of the infection. CIPRO should be administered as described in Table 3. Administer CIPRO for Oral Suspension using the co-packaged graduated spoon *[see Dosage and Administration (2.7)]*.

**Table 3: Pediatric Dosage Guidelines**

| Infection | Dose | Frequency | Total Duration |
|---|---|---|---|
| Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age) | 10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing more than 51 kg). | Every 12 hours | 10–21 days[1] |
| Inhalational Anthrax (Post-Exposure)[2] | 15 mg/kg (maximum 500 mg per dose) | Every 12 hours | 60 days |
| Plague[2,3] | 15 mg/kg (maximum 500 mg per dose) | Every 8 to 12 hours | 14 days |

1. The total duration of therapy for cUTI and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).
2. Begin drug administration as soon as possible after suspected or confirmed exposure.
3. Begin drug administration as soon as possible after suspected or confirmed exposure to *Y. pestis*.

## 2.3 Dosage Modifications in Patients with Renal Impairment

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, particularly for patients with severe renal dysfunction. Dosage guidelines for use in patients with renal impairment are shown in Table 4.

**Table 4: Recommended Starting and Maintenance Doses for Adult Patients with Impaired Renal Function**

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

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

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

Women - 0.85 x the value calculated for men.

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

In patients with severe infections and severe renal impairment, a unit dose of 750 mg may be administered at the intervals noted above. Patients should be carefully monitored.

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

## 2.4 Important Administration Instructions

*With Multivalent Cations*

Administer CIPRO at least 2 hours before or 6 hours after magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate) or sucralfate; Videx® (didanosine) chewable/buffered tablets or pediatric powder for oral solution; other highly buffered drugs; or other products containing calcium, iron or zinc.

*With Dairy Products*

Concomitant administration of CIPRO with dairy products (like milk or yogurt) or calcium-fortified juices alone should be avoided since decreased absorption is possible; however, CIPRO may be taken with a meal that contains these products.

*Hydration of Patients Receiving CIPRO*

Assure adequate hydration of patients receiving CIPRO to prevent the formation of highly concentrated urine. Crystalluria has been reported with quinolones.

Instruct the patient of the appropriate CIPRO administration *[see Patient Counseling Information (17)]*.

*Missed Doses*

If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

**2.5 Directions for Reconstitution of the CIPRO Microcapsules for Oral Suspension**

CIPRO Oral Suspension is supplied in 5% (5 g ciprofloxacin in 100 mL) and 10% (10 g ciprofloxacin in 100 mL) strengths. CIPRO oral suspension is composed of two components (microcapsules and diluent) that must be combined prior to dispensing.

**Table 5: Appropriate Dosing Volumes of the Reconstituted Oral Suspensions**

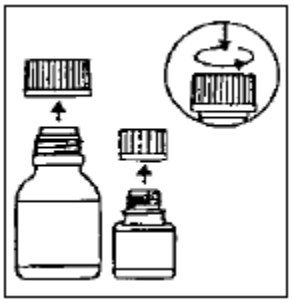
| **Dose** | **5%<br>(250 mg/5 mL)** | **10%<br>(500 mg/5 mL)** |
|---|---|---|
| 250 mg | 5 mL | 2.5 mL |
| 500 mg | 10 mL | 5 mL |
| 750 mg | 15 mL | 7.5 mL |

**Preparation of the suspension:**

Step1

The small bottle contains the microcapsules, the large bottle contains the diluent.

Step 2

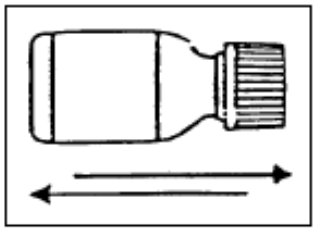


Open both bottles. Child-proof cap: Press down according to instructions on the cap while turning to the left.

Step 3

Pour the microcapsules completely into the larger bottle of diluent. **Do not add water to the suspension.**

Step 4



Remove the top layer of the diluent bottle label (to reveal the CIPRO Oral Suspension label). Close the large bottle completely according to the directions on the cap and shake vigorously for about 15 seconds. The suspension is ready for use.

Step 5: Write the expiration date of the re-constituted oral suspension on the bottle label.

Reconstituted product may be stored below 30°C (86°F) for 14 days. Protect from freezing.

No additions should be made to the mixed final ciprofloxacin suspension. CIPRO Oral Suspension should not be administered through feeding or NG (nasogastric) tubes due to its physical characteristics.

**2.6 Administration Instructions for CIPRO for Oral Suspension After Reconstitution**

- Shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds.
- Administer CIPRO Oral Suspension using the co-packaged graduated teaspoon provided for the patient (see Figure 1)

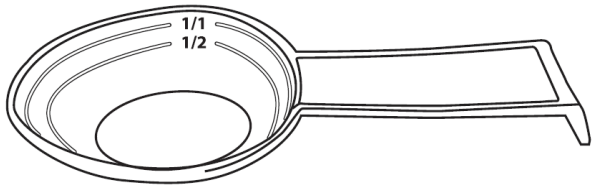



**Figure 1: Co-packaged 5 mL graduated teaspoon**

The Co-packaged graduated teaspoon (5mL) is provided, with markings for 1/2 (2.5 mL) and 1/1 (5 mL)

- After use, clean the graduated teaspoon under running water with dish detergent and dry thoroughly.
- Do Not chew the microcapsules in the CIPRO Oral Suspension, instead swallow them whole.
- Water may be taken afterwards.
- Reclose the bottle properly after each use according to instructions on the cap.
- After treatment has been completed, CIPRO Oral Suspension should not be reused.

### 2.7 Dosing of CIPRO for Oral Suspension using the Co-Packaged Spoon in Adults and Pediatric Patients

**Table 6: 5% Cipro for Oral Suspension: 250 mg ciprofloxacin per 5 mL after reconstitution**

| **Infection** | **Body weight (kg)** | **Dose by Measuring Spoonful(s) using Co-Packed Spoon* (teaspoonful (s) (volume (mL))** | **Dose Strength (mg)** |
|---|---|---|---|
| Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)[1] and Plague[2] | 9 kg to 12 kg | ½ teaspoonful (2.5 mL) | 125 mg |
| | 13 kg to 18 kg | 1 teaspoonful (5 mL) | 250 mg |
| | 19 kg to 24 kg | 1 to 1 ½ teaspoonful(s) (5 mL to 7.5 mL) | 250 mg to 375 mg |
| | 25 kg to 31 kg | 1 ½ to 2 teaspoonfuls (7.5 mL to 10 mL) | 375 mg to 500 mg |
| | 32 kg to 37 kg | 1 ½ to 2 ½ teaspoonfuls (7.5 mL to 12.5 mL) | 375 mg to 625 mg |
| | 38 kg or more | 2 to 3 teaspoonfuls (10 mL to 15 mL) | 500 mg to 750 mg |
| Inhalational Anthrax (Post-Exposure)[3] | 9 kg to 12 kg | ½ teaspoonful (2.5 mL) | 125 mg |
| | 13 kg to 18 kg | 1 teaspoonful (5 mL) | 250 mg |
| | 19 kg to 24 kg | 1 to 1 ½ teaspoonful(s) (5 mL to 7.5 mL) | 250 mg to 375 mg |
| | 25 kg or more | 2 teaspoonfuls (10 mL) | 500 mg |

### 5.8 Hepatotoxicity

Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with CIPRO. Acute liver injury is rapid in onset (range 1–39 days), and is often associated with hypersensitivity. The pattern of injury can be hepatocellular, cholestatic, or mixed. Most patients with fatal outcomes were older than 55 years old. In the event of any signs and symptoms of hepatitis (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), discontinue treatment immediately.

There can be a temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with CIPRO *[see Adverse Reactions (6.2, 6.3)]*.

### 5.9 Risk of Aortic Aneurysm and Dissection

Epidemiologic studies report an increased rate of aortic aneurysm and dissection within two months following use of fluoroquinolones, particularly in elderly patients. The cause for the increased risk has not been identified. In patients with a known aortic aneurysm or patients who are at greater risk for aortic aneurysms, reserve CIPRO for use only when there are no alternative antibacterial treatments available.

### 5.10 Serious Adverse Reactions with Concomitant Theophylline

Serious and fatal reactions have been reported in patients receiving concurrent administration of CIPRO and theophylline. These reactions have included cardiac arrest, seizure, status epilepticus, and respiratory failure. Instances of nausea, vomiting, tremor, irritability, or palpitation have also occurred.

Although similar serious adverse reactions have been reported in patients receiving theophylline alone, the possibility that these reactions may be potentiated by CIPRO cannot be eliminated. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate *[see Drug Interactions (7)]*.

### 5.11 *Clostridioides difficile*-Associated Diarrhea

*Clostridioides difficile (C. difficile)*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRO, 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 isolates 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 antibacterial 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 antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and institute surgical evaluation as clinically indicated *[see Adverse Reactions (6.1)]*.

### 5.12 Prolongation of the QT Interval

Some fluoroquinolones, including CIPRO, have been associated with prolongation of the QT interval on the electrocardiogram and cases of arrhythmia. Cases of torsade de pointes have been reported during postmarketing surveillance in patients receiving fluoroquinolones, including CIPRO.

Avoid CIPRO in patients with known prolongation of the QT interval, risk factors for QT prolongation or torsade de pointes (for example, congenital long QT syndrome, uncorrected electrolyte imbalance, such as hypokalemia or hypomagnesemia and cardiac disease, such as heart failure, myocardial infarction, or bradycardia), and patients receiving Class IA antiarrhythmic agents (quinidine, procainamide), or Class III antiarrhythmic agents (amiodarone, sotalol), tricyclic antidepressants, macrolides, and antipsychotics. Elderly patients may also be more susceptible to drug-associated effects on the QT interval *[see Adverse Reactions (6.2), Use in Specific Populations (8.5)]*.

### 5.13 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

CIPRO is indicated in pediatric patients (less than 18 years of age) only for cUTI, prevention of inhalational anthrax (post exposure), and plague *[see Indications and Usage (1.7, 1.8, 1.11)]*. An increased incidence of adverse reactions compared to controls, including reactions related to joints and/or surrounding tissues, has been observed *[see Adverse Reactions (6.1)]*.

In pre-clinical studies, oral administration of CIPRO 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 Use in Specific Populations (8.4) and Nonclinical Toxicology (13.2)]*.

### 5.14 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 including CIPRO after sun or UV light exposure. Therefore, avoid excessive exposure to these sources of light. Discontinue CIPRO if phototoxicity occurs *[see Adverse Reactions (6.1)]*.

### 5.15 Development of Drug Resistant Bacteria

Prescribing CIPRO Tablets and CIPRO Oral Suspension 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.

### 5.16 Potential Risks with Concomitant Use of Drugs Metabolized by Cytochrome P450 1A2 Enzymes

CIPRO is an inhibitor of the hepatic CYP1A2 enzyme pathway. Co-administration of CIPRO and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine and zolpidem), results in increased plasma concentrations of the co-administered drug and could lead to clinically significant pharmacodynamic adverse reactions of the co-administered drug *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

### 5.17 Interference with Timely Diagnosis of Syphilis

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

### 5.18 Crystalluria

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 Nonclinical Toxicology (13.2)]*. Crystalluria related to CIPRO has been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving CIPRO. Hydrate patients well to prevent the formation of highly concentrated urine *[see Dosage and Administration (2.4)]*.

### 5.19 Blood Glucose Disturbances

Fluoroquinolones, including CIPRO, have been associated with disturbances of blood glucose, including symptomatic hyperglycemia and hypoglycemia, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (for example, glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. Severe cases of hypoglycemia resulting in coma or death have been reported. If a hypoglycemic reaction occurs in a patient being treated with CIPRO, discontinue CIPRO and initiate appropriate therapy immediately *[see Adverse Reactions (6.1), Drug Interactions (7)]*.

# 6 ADVERSE REACTIONS

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

- Disabling and Potentially Irreversible Serious Adverse Reactions *[see Warnings and Precautions (5.1)]*
- Tendinitis and Tendon Rupture *[see Warnings and Precautions (5.2)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.3)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.4)]* Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (5.5)]*
- Other Serious and Sometimes Fatal Adverse Reactions *[see Warnings and Precautions (5.6)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.7)]*
- Hepatotoxicity *[see Warnings and Precautions (5.8)]*
- Risk of Aortic Aneurysm and Dissection *[see Warnings and Precautions (5.9)]*
- Serious Adverse Reactions with Concomitant Theophylline *[see Warnings and Precautions (5.10)]*
- *Clostridioides difficile*-Associated Diarrhea *[see Warnings and Precautions (5.11)]*
- Prolongation of the QT Interval *[see Warnings and Precautions (5.12)]*
- Musculoskeletal Disorders in Pediatric Patients *[see Warnings and Precautions (5.13)]*
- Photosensitivity/Phototoxicity *[see Warnings and Precautions (5.14)]*
- Development of Drug Resistant Bacteria *[see Warnings and Precautions (5.15)]*

## 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

*Adult Patients*

During clinical investigations with oral and parenteral CIPRO, 49,038 patients received courses of the drug.

The most frequently reported adverse reactions, 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%), and rash (1%).

**Table 8: Medically Important Adverse Reactions That Occurred in less than 1% of Ciprofloxacin Patients**

| System Organ Class | Adverse Reactions |
|---|---|
| **Body as a Whole** | Headache<br>Abdominal Pain/Discomfort<br>Pain |
| **Cardiovascular** | Syncope<br>Angina Pectoris<br>Myocardial Infarction<br>Cardiopulmonary Arrest<br>Tachycardia<br>Hypotension |
| **Central Nervous System** | Restlessness<br>Dizziness<br>Insomnia<br>Nightmares<br>Hallucinations<br>Paranoia<br>Psychosis (toxic)<br>Manic Reaction<br>Irritability<br>Tremor<br>Ataxia<br>Seizures (including Status Epilepticus)<br>Malaise<br>Anorexia<br>Phobia<br>Depersonalization<br>Depression (potentially culminating in self-injurious behavior<br>(such as suicidal ideations/thoughts and attempted or completed suicide)<br>Paresthesia<br>Abnormal Gait<br>Migraine |
| **Gastrointestinal** | Intestinal Perforation<br>Gastrointestinal Bleeding<br>Cholestatic Jaundice<br>Hepatitis<br>Pancreatitis |
| **Hemic/Lymphatic** | Petechia |
| **Metabolic/Nutritional** | Hyperglycemia<br>Hypoglycemia |
| **Musculoskeletal** | Arthralgia<br>Joint Stiffness<br>Muscle Weakness |
| **Renal/Urogenital** | Interstitial Nephritis<br>Renal Failure |
| **Respiratory** | Dyspnea<br>Laryngeal Edema<br>Hemoptysis<br>Bronchospasm |

| | |
|---|---|
| **Skin/Hypersensitivity** | Anaphylactic Reactions including life-threatening anaphylactic shock<br>Erythema Multiforme/Stevens-Johnson Syndrome<br>Exfoliative Dermatitis<br>Toxic Epidermal Necrolysis<br>Pruritus<br>Urticaria<br>Photosensitivity/Phototoxicity reaction<br>Flushing<br>Fever<br>Angioedema<br>Erythema Nodosum<br>Sweating |
| **Special Senses** | Blurred Vision<br>Disturbed Vision (chromatopsia and photopsia)<br>Decreased Visual Acuity<br>Diplopia<br>Tinnitus<br>Hearing Loss<br>Bad Taste |

In randomized, double-blind controlled clinical trials comparing CIPRO tablets [500 mg two times daily (BID)] to cefuroxime axetil (250 mg–500 mg BID) and to clarithromycin (500 mg BID) in patients with respiratory tract infections, CIPRO demonstrated a CNS adverse reaction profile comparable to the control drugs.

*Pediatric Patients*

Short (6 weeks) and long term (1 year) musculoskeletal and neurological safety of oral/intravenous ciprofloxacin, was compared to a cephalosporin for treatment of cUTI or pyelonephritis in pediatric patients 1 to 17 years of age (mean age of 6 ± 4 years) in an international multicenter trial. The duration of therapy was 10 to 21 days (mean duration of treatment was 11 days with a range of 1 to 88 days). A total of 335 ciprofloxacin- and 349 comparator-treated patients were enrolled.

An Independent Pediatric Safety Committee (IPSC) reviewed all cases of musculoskeletal adverse reactions including abnormal gait or abnormal joint exam (baseline or treatment-emergent). Within 6 weeks of treatment initiation, the rates of musculoskeletal adverse reactions were 9.3% (31/335) in the ciprofloxacin-treated group versus 6% (21/349) in comparator-treated patients. All musculoskeletal adverse reactions 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 adverse reactions. Ciprofloxacin-treated patients were more likely to report more than one adverse reaction and on more than one occasion compared to control patients. The rate of musculoskeletal adverse reactions was consistently higher in the ciprofloxacin group compared to the control group across all age subgroups. At the end of 1 year, the rate of these adverse reactions reported at any time during that period was 13.7% (46/335) in the ciprofloxacin-treated group versus 9.5% (33/349) in the comparator-treated patients (Table 9).

**Table 9: Musculoskeletal Adverse Reactions[1] as Assessed by the IPSC**

| | CIPRO | Comparator |
|---|---|---|
| All Patients (within 6 weeks) | 31/335 (9.3%) | 21/349 (6%) |
| 95% Confidence Interval[2] | (-0.8%, +7.2%) | |
| Age Group | | |
| 12 months < 24 months | 1/36 (2.8%) | 0/41 |
| 2 years < 6 years | 5/124 (4%) | 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[1] | (-0.6%, + 9.1%) | |

1. Included: 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 (knee, elbow, ankle, hip, wrist, and shoulder)
2. 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 adverse reactions within 6 weeks of treatment initiation were 3% (9/335) in the CIPRO 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 reactions 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 adverse reactions were gastrointestinal: 15% (50/335) of ciprofloxacin patients compared to 9% (31/349) of comparator patients. Serious adverse reactions 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 reaction was observed in 3% (10/335) of ciprofloxacin-treated patients versus 1.4% (5/349) of comparator patients. Other adverse reactions that occurred in at least 1% of ciprofloxacin patients were diarrhea 4.8%, vomiting 4.8%, abdominal pain 3.3%, dyspepsia 2.7%, nausea 2.7%, fever 2.1%, asthma 1.8% and rash 1.8%.

Short-term safety data for ciprofloxacin was also collected in a randomized, double-blind clinical trial for the treatment of acute pulmonary exacerbations in cystic fibrosis patients (ages 5–17 years). Sixty-seven patients received CIPRO IV 10 mg/kg/dose every 8 hours for one week followed by CIPRO tablets 20 mg/kg/dose every 12 hours to complete 10–21 days treatment and 62 patients received the combination of ceftazidime intravenous 50 mg/kg/dose every 8 hours and tobramycin intravenous 3 mg/kg/dose every 8 hours for a total of 10–21 days. Periodic musculoskeletal assessments were conducted by treatment-blinded examiners. Patients were followed for an average of 23 days after completing treatment (range 0–93 days). Musculoskeletal adverse reactions 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 reactions were similar in nature and frequency between treatment arms. The efficacy of CIPRO for the treatment of acute pulmonary exacerbations in pediatric cystic fibrosis patients has not been established.

In addition to the adverse reactions reported in pediatric patients in clinical trials, it should be expected that adverse reactions reported in adults during clinical trials or postmarketing experience may also occur in pediatric patients.

## 6.2 Postmarketing Experience

The following adverse reactions have been reported from worldwide marketing experience with fluoroquinolones, including CIPRO. Because these reactions 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 (Table 10).

**Table 10: Postmarketing Reports of Adverse Drug Reactions**

| System Organ Class | Adverse Reactions |
|---|---|
| **Cardiovascular** | QT prolongation<br>Torsade de Pointes<br>Vasculitis and ventricular arrhythmia |
| **Central Nervous System** | Hypertonia<br>Myasthenia<br>Exacerbation of myasthenia gravis<br>Peripheral neuropathy<br>Polyneuropathy<br>Twitching |
| **Eye Disorders** | Nystagmus |
| **Gastrointestinal** | Pseudomembranous colitis |
| **Hemic/Lymphatic** | Pancytopenia (life threatening or fatal outcome)<br>Methemoglobinemia |
| **Hepatobiliary** | Hepatic failure (including fatal cases) |
| **Infections and Infestations** | Candidiasis (oral, gastrointestinal, vaginal) |
| **Investigations** | Prothrombin time prolongation or decrease<br>Cholesterol elevation (serum)<br>Potassium elevation (serum) |
| **Musculoskeletal** | Myalgia<br>Myoclonus<br>Tendinitis<br>Tendon rupture |
| **Psychiatric Disorders** | Agitation<br>Confusion<br>Delirium |
| **Skin/Hypersensitivity** | Acute generalize exanthematous pustulosis (AGEP)<br>Fixed eruption<br>Serum sickness-like reaction |
| **Special Senses** | Anosmia<br>Hyperesthesia<br>Hypesthesia<br>Taste loss |

## 6.3 Adverse Laboratory Changes

Changes in laboratory parameters while on CIPRO are listed below:

Hepatic –Elevations of ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, serum bilirubin.

Hematologic–Eosinophilia, leukopenia, decreased blood platelets, elevated blood platelets, pancytopenia.

Renal–Elevations of serum creatinine, BUN, crystalluria, cylindruria, and hematuria have been reported.

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

one of the following 5 day periods: GD 6 to 10, GD 10 to 14, or GD 14 to 18, intended to cover the period of organogenesis. This was an attempt to mitigate the gastrointestinal intolerance observed in rabbits that receive antibacterials manifested by reduced maternal food consumption and weight loss, that can lead to embryofetal resorption or spontaneous abortion. An oral ciprofloxacin dose of 100 mg/kg (approximately 1.3 times the highest recommended clinical oral dose based on body surface area) caused excessive maternal toxicity confounding evaluation of the fetuses. A 30 mg/kg oral dose (approximately 0.4 times the highest recommended clinical oral dose) was associated with suppression of maternal and fetal body weight gain, but fetal malformations were not observed. Intravenous administration of doses up to 20 mg/kg (approximately 0.3 times the highest recommended clinical oral dose based upon body surface area) to pregnant rabbits was not maternally toxic and neither embryofetal toxicity nor fetal malformations were observed.

In peri- and post-natal studies, rats received ciprofloxacin doses up to 200 mg/kg/day (oral) or up to 30 mg/kg/day (subcutaneous) from GD 16 to 22 days postpartum. The 200 mg/kg dose is approximately 1.3-times the maximum recommended clinical oral dose based on body surface area. Neither maternal toxicity nor adverse effects on growth and development of the pups were observed, including no sign of arthropathy on the rear leg joints of the pups. Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested when administered directly *[see Warnings and Precautions (5.13) and Nonclinical Toxicology 13.2]*.

## 8.2 Lactation

*Risk Summary*

Published literature reports that ciprofloxacin is present in human milk following intravenous and oral administration. There is no information regarding effects of CIPRO on milk production or the breastfed infant. Because of the potential risk of serious adverse reactions in breastfed infants, including arthropathy shown in juvenile animal studies *[see Use in Specific Populations (8.4), (Clinical Considerations)]*, for most indications a lactating woman may consider pumping and discarding breast milk during treatment with CIPRO and an additional two days (five half-lives) after the last dose. Alternatively, advise a woman that breastfeeding is not recommended during treatment with CIPRO and for an additional two days (five half-lives) after the last dose.

However, for inhalation anthrax (post exposure), during an incident resulting in exposure to anthrax, the risk-benefit assessment of continuing breastfeeding while the mother (and potentially the infant) is (are) on CIPRO may be acceptable *[see Dosage and Administration (2.2), Pediatric Use (8.4), and Clinical Studies (14.2)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CIPRO and any potential adverse effects on the breastfed child from CIPRO or from the underlying maternal condition.

*Clinical Considerations*

Ciprofloxacin may cause intestinal flora alteration of the breastfeeding infant. Advise a woman to monitor the breastfed infant for loose or bloody stools and candidiasis (thrush, diaper rash).

## 8.4 Pediatric Use

Although effective in clinical trials, CIPRO is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls. Quinolones, including CIPRO, cause arthropathy (arthralgia, arthritis), in juvenile animals *[see Warnings and Precautions (5.13) and Nonclinical Toxicology (13.2)]*.

*Complicated Urinary Tract Infection and Pyelonephritis*

CIPRO is indicated for the treatment of cUTI and pyelonephritis due to *Escherichia coli* in pediatric patients 1 to 17 years of age. Although effective in clinical trials, CIPRO is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to the controls, including events related to joints and/or surrounding tissues *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

*Inhalational Anthrax (Post-Exposure)*

CIPRO is indicated in pediatric patients from birth to 17 years of age, for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate *[see Dosage and Administration (2.2) and Clinical Studies (14.2)]*.

*Plague*

CIPRO is indicated in pediatric patients from birth to 17 years of age, for treatment of plague, including pneumonic and septicemic plague due to *Yersinia pestis (Y. pestis)* and prophylaxis for plague. Efficacy studies of CIPRO could not be conducted in humans with pneumonic plague for feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The risk-benefit assessment indicates that administration of CIPRO to pediatric patients is appropriate *[see Indications and Usage (1.8), Dosage and Administration (2.2) and Clinical Studies (14.3)]*.

## 8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRO. 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 CIPRO to elderly patients especially those on corticosteroids. Patients should be informed of this potential adverse reaction and advised to discontinue CIPRO and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur *[see Boxed Warning, Warnings and Precautions (5.2), and Adverse Reactions (6.2)]*.

Epidemiologic studies report an increased rate of aortic aneurysm and dissection within two months following use of fluoroquinolones, particularly in elderly patients *[see Warnings and Precautions (5.9)]*.

In a retrospective analysis of 23 multiple-dose controlled clinical trials of CIPRO 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 Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using CIPRO 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) *[see Warnings and Precautions (5.12)]*.

## 8.6 Renal Impairment

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, particularly for patients with severe renal dysfunction *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

# 12 CLINICAL PHARMACOLOGY

## 12.1 Mechanism of Action

Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents *[see Microbiology (12.4)]*.

## 12.3 Pharmacokinetics

*Absorption*

The absolute bioavailability of ciprofloxacin when given as an oral tablet is approximately 70% with no substantial loss by first pass metabolism. Ciprofloxacin maximum serum concentrations ($C_{max}$) and area under the curve (AUC) are shown in the chart for the 250 mg to 1000 mg dose range (Table 12).

**Table 12: Ciprofloxacin Cmax and AUC Following Adminstration of Single Doses of CIPRO Tablets to Healthy Subjects**

| Dose (mg) | Cmax (mcg/mL) | AUC (mcg•hr/mL) |
|---|---|---|
| 250 | 1.2 | 4.8 |
| 500 | 2.4 | 11.6 |
| 750 | 4.3 | 20.2 |
| 1000 | 5.4 | 30.8 |

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500, or 750 mg are 0.1, 0.2, and 0.4 mcg/mL, respectively. The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Serum concentrations increase proportionately with doses up to 1000 mg.

A 500 mg oral dose given every 12 hours has been shown to produce an AUC equivalent to that produced by an intravenous infusion of 400 mg CIPRO given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at steady-state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a $C_{max}$ similar to that observed with a 400 mg intravenous dose (Table 13). A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg CIPRO given every 12 hours.

**Table 13: Steady-state Pharmacokinetic Parameters Following Multiple Oral and Intravenous Doses (Adults)**

| Parameters | 500 mg | 400 mg | 750 mg | 400 mg |
|---|---|---|---|---|
| | every 12 hours, orally | every 12 hours, intravenously | every 12 hours, orally | every 8 hours, intravenously |
| $AUC_{0\text{-}24h,ss}$ (µg•h/mL) | 27.4* | 25.4* | 31.6* | 32.9** |
| $C_{max,ss}$ (µg/mL) | 2.97 | 4.56 | 3.59 | 4.07 |

*: $AUC_{0\text{-}12h}$ x 2
**: $AUC_{0\text{-}8h}$ x 3

Food

When CIPRO Tablet is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather than 1 hour whereas there is no delay observed when

Ropinirole

In a study conducted in 12 patients with Parkinson's disease who were administered 6 mg ropinirole once daily with 500 mg CIPRO twice-daily, the mean $C_{max}$ and mean AUC of ropinirole were increased by 60% and 84%, respectively. Monitoring for ropinirole-related adverse reactions and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with CIPRO *[see Warnings and Precautions (5.10)]*.

Clozapine

Following concomitant administration of 250 mg CIPRO 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 reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIPRO are advised.

Sildenafil

Following concomitant administration of a single oral dose of 50 mg sildenafil with 500 mg CIPRO to healthy subjects, the mean $C_{max}$ and mean AUC of sildenafil were both increased approximately two-fold. Use sildenafil with caution when co-administered with CIPRO due to the expected two-fold increase in the exposure of sildenafil upon co-administration of CIPRO.

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 in mean AUC and a 2.5-fold increase in mean $C_{max}$ of duloxetine.

Lidocaine

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

Metoclopramide

Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

Omeprazole

When CIPRO was administered as a single 1000 mg dose concomitantly with omeprazole (40 mg once daily for three days) to 18 healthy volunteers, the mean AUC and $C_{max}$ of ciprofloxacin were reduced by 20% and 23%, respectively. The clinical significance of this interaction has not been determined.

## 12.4 Microbiology

*Mechanism of Action*

The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV (both Type II topoisomerases), 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 mutations 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 mutations 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 *[see Indications and Usage (1)]*.

Gram-positive bacteria

*Bacillus anthracis*

*Enterococcus faecalis*

*Staphylococcus aureus* (methicillin-susceptible isolates only)

*Staphylococcus epidermidis* (methicillin-susceptible isolates only)

*Staphylococcus saprophyticus*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

Gram-negative bacteria

*Campylobacter jejuni*

*Citrobacter koseri*

*Citrobacter freundii*

*Enterobacter cloacae*

*Escherichia coli*

*Haemophilus influenzae*

*Haemophilus parainfluenzae*

*Klebsiella pneumoniae*

*Moraxella catarrhalis*

*Morganella morganii*

*Neisseria gonorrhoeae*

*Proteus mirabilis*

*Proteus vulgaris*

*Providencia rettgeri*

*Providencia stuartii*

*Pseudomonas aeruginosa*

*Salmonella typhi*

*Serratia marcescens*

*Shigella boydii*

*Shigella dysenteriae*

*Shigella flexneri*

*Shigella sonnei*

*Yersinia pestis*

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 concentration (MIC) less than or equal to the susceptible breakpoint for ciprofloxacin against isolates of similar genus or organism group. However, the efficacy of ciprofloxacin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

*Staphylococcus haemolyticus* (methicillin-susceptible isolates only)

*Staphylococcus hominis* (methicillin-susceptible isolates only)

Gram-negative bacteria

*Acinetobacter lwoffi*

*Aeromonas hydrophila*

*Edwardsiella tarda*

*Enterobacter aerogenes*

*Klebsiella oxytoca*

*Legionella pneumophila*

*Pasteurella multocida*

*Salmonella enteritidis*

*Vibrio cholerae*

*Vibrio parahaemolyticus*

*Vibrio vulnificus*

*Yersinia enterocolitica*

*Susceptibility Testing*

For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

# 13 NONCLINICAL TOXICOLOGY

## 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

- Rat Hepatocyte DNA Repair Assay

- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in rats and mice resulted in no carcinogenic or tumorigenic effects due to ciprofloxacin at daily oral dose levels up to 250 mg/kg and 750 mg/kg to rats and mice, respectively (approximately 1.7- and 2.5- times the highest recommended therapeutic dose based upon body surface area, respectively).

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 body surface area), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumors ranged from 16 weeks to 32 weeks in mice treated concomitantly with UVA and other quinolones.[5]

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 male and female rats at oral doses of ciprofloxacin up to 100 mg/kg (approximately 0.6 times the highest recommended therapeutic oral dose based upon body surface area) revealed no evidence of impairment. Male rats received oral ciprofloxacin for 10 weeks prior to mating and females were dosed for 3 weeks prior to mating through Gestation Day 7.

### 13.2 Animal Toxicology and/or Pharmacology

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested *[see Warnings and Precautions (5.13)]*. 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-times 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 body surface area). 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 body surface area).

In dogs, ciprofloxacin at 3 mg/kg and 10 mg/kg by rapid intravenous injection (15 sec.) produces pronounced hypotensive effects. These effects are considered to be related to histamine release, since they are partially antagonized by pyrilamine, an antihistamine. In rhesus monkeys, rapid 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

# 14 CLINICAL STUDIES

## 14.1 Complicated Urinary Tract Infection and Pyelonephritis–Efficacy in Pediatric Patients

CIPRO administered intravenously and/or orally was compared to a cephalosporin for treatment of 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 CIPRO and the comparator group as shown below.

**Table 15: Clinical Success and Bacteriologic Eradication at Test of Cure (5 to 9 Days Post-Therapy)**

| | **CIPRO** | **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[1] | 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%) |

1. 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.

## 14.2 Inhalational Anthrax in Adults and Pediatrics

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. 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 mcg/mL 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 CIPRO to pediatric

patients are limited. Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.[1]

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 $LD_{50}$ (~5.5 x $10^5$ spores (range 5–30 $LD_{50}$) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 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 mcg/mL to 1.69 mcg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 mcg/mL to 0.19 mcg/mL.[6] 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 CIPRO-treated animal that died of anthrax did so following the 30-day drug administration period.[7]

More than 9300 persons were recommended to complete a minimum of 60 days of antibacterial prophylaxis against possible inhalational exposure to *B. anthracis* during 2001. CIPRO 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 antibacterial drugs. No one who received CIPRO or other therapies as prophylactic treatment subsequently developed inhalational anthrax. The number of persons who received CIPRO as all or part of their post-exposure prophylaxis regimen is unknown.

### 14.3 Plague

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 110 $LD_{50}$ (range 92 to 127 $LD_{50}$) of *Yersinia pestis* (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the *Y. pestis* strain used in this study was 0.015 mcg/mL. Mean peak serum concentrations of ciprofloxacin achieved at the end of a single 60 minute infusion were 3.49 ± mcg/mL 0.55 mcg/mL, 3.91 mcg/mL ± 0.58 mcg/mL and 4.03 mcg/mL ± 1.22 mcg/mL on Day 2, Day 6 and Day 10 of treatment in African green monkeys, respectively All trough concentrations (Day 2, Day 6 and Day 10) were <0.5 mcg /mL. Animals were randomized to receive either a 10-day regimen of intravenous ciprofloxacin 15 mg/kg, or placebo beginning when animals were found to be febrile (a body temperature greater than 1.5° C over baseline for two hours), or at 76 hours post-challenge, whichever occurred sooner. Mortality in the ciprofloxacin group was significantly lower (1/10) compared to the placebo group (2/2) [difference: -90.0%, 95% exact confidence interval: -99.8% to -5.8%]. The one ciprofloxacin-treated animal that died did not receive the proposed dose of ciprofloxacin due to a failure of the administration catheter. Circulating ciprofloxacin concentration was below 0.5 mcg/mL at all timepoints tested in this animal. It became culture negative on Day 2 of treatment, but had a resurgence of low grade bacteremia on Day 6 after treatment initiation. Terminal blood culture in this animal was negative.[8]

## 15 REFERENCES


1. 21 CFR 314.510 (Subpart H–Accelerated Approval of New Drugs for Life-Threatening Illnesses).
2. Friedman J, Polifka J. Teratogenic effects of drugs: a resource for clinicians (TERIS). Baltimore, Maryland: Johns Hopkins University Press, 2000:149-195.
3. Loebstein R, Addis A, Ho E, et al. Pregnancy outcome following gestational exposure to fluoroquinolones: a multicenter prospective controlled study. Antimicrob Agents Chemother. 1998;42(6):1336-1339.
4. Schaefer C, Amoura-Elefant E, Vial T, et al. Pregnancy outcome after prenatal quinolone exposure. Evaluation of a case registry of the European network of teratology information services (ENTIS). Eur J Obstet Gynecol Reprod Biol. 1996;69:83-89.
5. Report presented at the FDA's Anti-Infective Drug and Dermatological Drug Product's Advisory Committee meeting, March 31, 1993, Silver Spring, MD. Report available from FDA, CDER, Advisors and Consultants Staff, HFD-21, 1901 Chapman Avenue, Room 200, Rockville, MD 20852, USA.

the same patient. Inform patients to stop taking CIPRO immediately if they experience an adverse reaction and to call their healthcare provider.

- **Tendinitis and tendon rupture:** Instruct patients 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 CIPRO treatment. Symptoms may be irreversible. 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.
- **Peripheral Neuropathies:** Inform patients that peripheral neuropathies have been associated with ciprofloxacin use, symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, immediately discontinue CIPRO and tell them to contact their physician.
- **Central nervous system effects** (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure)**:** Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including Ciprofloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to CIPRO before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.
- **Exacerbation of Myasthenia Gravis:** Instruct patients to inform their physician of any history of myasthenia gravis. Instruct patients to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions:** Inform patients that ciprofloxacin can cause hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Hepatotoxicity:** Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking CIPRO. Instruct patients to inform their physician if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.
- **Aortic aneurysm and dissection:** Inform patients to seek emergency medical care if they experience sudden chest, stomach, or back pain.
- **Diarrhea:** 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, instruct patients to contact their physician as soon as possible.
- **Prolongation of the QT Interval:** Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Instruct patients to notify their physician if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.
- **Musculoskeletal Disorders in Pediatric Patients:** Instruct parents to inform their child's physician if the child has a history of joint-related problems before taking this drug. Inform parents of pediatric patients to notify their child's physician of any joint-related problems that occur during or following ciprofloxacin therapy *[see Warnings and Precautions (5.13) and Use in Specific Populations (8.4)]*.

- **Tizanidine:** Instruct patients not to use ciprofloxacin if they are already taking tizanidine. CIPRO increases the effects of tizanidine (Zanaflex®).
- **Theophylline:** Inform patients that ciprofloxacin CIPRO may increase the effects of theophylline. Life-threatening CNS effects and arrhythmias can occur. Advise the patients to immediately seek medical help if they experience seizures, palpitations, or difficulty breathing.
- **Caffeine:** Inform patients that CIPRO may increase the effects of caffeine. There is a possibility of caffeine accumulation when products containing caffeine are consumed while taking quinolones.
- **Photosensitivity/Phototoxicity:** Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Inform patients to 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, instruct them to 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, instruct patients to contact their physician.
- **Blood Glucose Disturbances:** Inform the patients that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue CIPRO and consult a physician.
- **Lactation:** For indications other than inhalational anthrax (post exposure), advise a woman that breastfeeding is not recommended during treatment with Cipro and for an additional 2 days after the last dose. Alternatively, a woman may pump and discard during treatment and for additional 2 days after the last dose *[see Use in Specific Populations (8.2)]*.

**Antibacterial Resistance**

Inform patients that antibacterial drugs including CIPRO Tablets and CIPRO Oral Suspension should only be used to treat bacterial infections. They do not treat viral infections (for example, the common cold). When CIPRO Tablets and CIPRO Oral Suspension are 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 CIPRO Tablets and CIPRO Oral Suspension or other antibacterial drugs in the future.

**Administration Instructions**

*Instruct the Patient*

- To shake CIPRO Oral Suspension vigorously each time before use for approximately 15 seconds.
- To always use the co-packaged graduated measuring spoon with markings for 1/2 (2.5 mL) and 1/1 (5 mL), to obtain the exact dose.
- After use, the graduated measuring spoon should be cleaned under running water with dish detergent and dried thoroughly.
- Not to chew the microcapsules, but to swallow them whole.
- That water may be taken afterwards.
- Reclose the bottle properly after each use according to instructions on the cap.
- After treatment has been completed, CIPRO Oral Suspension should not be reused.

Inform patients that CIPRO may be taken with or without food.

Inform patients to drink fluids liberally while taking CIPRO to avoid formation of highly concentrated urine and crystal formation in the urine.

Inform patients that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine should be taken at least two hours before or six hours after CIPRO administration. CIPRO should not be taken with dairy products (like milk or yogurt) or calcium-fortified juices alone since absorption of ciprofloxacin may be significantly reduced; however, CIPRO may be taken with a meal that contains these products.

Advise patients that if a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

**Drug Interactions Oral Antidiabetic Agents**

Inform patients that hypoglycemia has been reported when ciprofloxacin and oral antidiabetic agents were co-administered; if low blood sugar occurs with CIPRO, instruct them to consult their physician and that their antibacterial medicine may need to be changed.

**Anthrax and Plague Studies**

Inform patients given CIPRO for these conditions that efficacy studies could not be conducted in humans for feasibility reasons. Therefore, approval for these conditions was based on efficacy studies conducted in animals.

**Medication Guide**

**CIPRO® (Sip-row)**
(ciprofloxacin hydrochloride)
tablets, for oral use

**CIPRO® (Sip-row)**
(ciprofloxacin)
for oral suspension

**CIPRO® XR (Sip-row)**
(ciprofloxacin)
extended-release tablets, for oral use

**CIPRO® IV (Sip-row)**
(ciprofloxacin)
injection, for intravenous infusion

Read this Medication Guide before you start taking CIPRO and each time you get a refill. There may be new information. This information 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 CIPRO?**

**CIPRO, a fluoroquinolone antibacterial medicine, can cause serious side effects. Some of these serious side effects can happen at the same time and could result in death.**

If you get any of the following serious side effects while you take CIPRO, you should stop taking CIPRO immediately and get medical help right away.

1. **Tendon rupture or swelling of the tendon (tendinitis).**
   - **Tendon problems can happen in people of all ages who take CIPRO.** Tendons are tough cords of tissue that connect muscles to bones. **Symptoms of tendon problems may include:**
     - pain
     - swelling
     - tears and swelling of the tendons including the back of the ankle (Achilles), shoulder, hand, thumb, or other tendon sites.
   - **The risk of getting tendon problems while you take CIPRO 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 CIPRO.**
   - **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).
   - **Stop taking CIPRO immediately and get medical help right away at the first sign of tendon pain, swelling or inflammation.** 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.
   - **Tendon rupture can happen while you are taking or after you have finished taking CIPRO.** Tendon ruptures can happen within hours or days of taking CIPRO and have happened up to several months after people have finished taking their fluoroquinolone.
   - **Stop taking CIPRO immediately and 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

   The tendon problems may be permanent.

2. **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 CIPRO. Stop taking CIPRO