Summary of Product Characteristics (SmPC)

1. Name of the medicinal product
CIPROGYL IV
(Ciprofloxacin Injection USP 200 mg/ 100 mL)

2. Qualitative and quantitative composition
Each 100 mL contains
Ciprofloxacin Hydrochloride USP
Equivalent to Ciprofloxacin…….200 mg
Sodium Chloride USP……..0.9% w/v
Water for Injection USP……q.s.

3. Pharmaceutical form
Injection

4. Clinical particulars

4.1 Therapeutic indications
Skin and Skin Structure Infections
Ciprofloxacin 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*.
Bone and Joint Infections
Ciprofloxacin is indicated in adult patients for treatment of bone and joint infections caused by *Enterobacter cloacae*, *Serratia marcescens,* or *Pseudomonas aeruginosa*.
Complicated Intra-Abdominal Infections
Ciprofloxacin 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*.
Nosocomial Pneumonia
Ciprofloxacin is indicated in adult patients for treatment of nosocomial pneumonia caused by *Haemophilus influenzae* or *Klebsiella pneumoniae*.
Empirical Therapy for Febrile Neutropenic Patients
Ciprofloxacin is indicated in adult patients for the treatment of febrile neutropenia in combination with piperacillin sodium.
Inhalational Anthrax (Post-Exposure)
Ciprofloxacin is indicated in adults and pediatric patients from birth to 17 years of age for treatment of 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. Supportive clinical information for ciprofloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001.

Plague
Ciprofloxacin 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.

Chronic Bacterial Prostatitis

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

Lower Respiratory Tract Infections

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

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

Because fluoroquinolones, including ciprofloxacin, have been associated with serious adverse reactions and for some patients AECB is self-limiting, reserve ciprofloxacin for treatment of AECB in patients who have no alternative treatment options.

Urinary Tract Infections

Urinary Tract Infection in Adults

Ciprofloxacin 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*.

Complicated Urinary Tract Infections and Pyelonephritis in Pediatric Patients

Ciprofloxacin is indicated in pediatric patients one to 17 years of age for treatment of complicated urinary tract infections (cUTI) 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 reactions compared to controls, including reactions related to joints and/or surrounding tissues. Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals.

Acute Sinusitis

Ciprofloxacin is indicated in adult patients for treatment of acute sinusitis caused by *Haemophilus influenzae, Streptococcus pneumoniae*, or *Moraxella catarrhalis*. Because fluoroquinolones, including ciprofloxacin, have been associated with serious adverse reactions and for some patients acute sinusitis is self-limiting, reserve ciprofloxacin for treatment of acute sinusitis in patients who have no alternative treatment options.

Usage

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

4.2 Posology and method of administration

Ciprofloxacin Injection, USP should be administered intravenously at dosages described in the appropriate Dosage Guidelines tables.

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.

Table 1: Adult Dosage Guidelines

Infection*	**Dose**	**Frequency**	**Usual duration**
Skin and skin structure	400 mg	every 8 to 12 hours	7–14 days
Bone and Joint	400 mg	every 8 to 12 hours	4 to 8 weeks
Complicated Intra-Abdominal†	400 mg	every 12 hours	7–14 days
Nosocomial Pneumonia	400 mg	every 8 hours	10–14 days
Empirical Therapy In Febrile Neutropenic Patients	Ciprofloxacin 400 mg And Piperacillin 50 mg/kg	every 8 hours every 4 hours	7–14 days
Inhalational Anthrax (Post-Exposure) ‡	400 mg	every 12 hours	60 days
Plague‡	400 mg	every 8 to 12 hours	14 days
Chronic Bacterial Prostatitis	400 mg	every 12 hours	28 days
Lower Respiratory Tract Infections	400 mg	every 8 to 12 hours	7–14 days
Urinary Tract Infections	200 mg to 400 mg	every 8 to 12 hours	7–14 days
Acute Sinusitis	400 mg	every 12 hours	10 days

*****Due to the designated pathogens

† Used in conjunction with metronidazole.

‡ Begin administration as soon as possible after suspected or confirmed exposure.

Conversion of Intravenous to Oral Dosing in Adults

Patients whose therapy is started with ciprofloxacin injection may be switched to ciprofloxacin Tablets or Oral Suspension when clinically indicated at the discretion of the physician.

Table 2: Equivalent AUC Dosing Regimens

Ciprofloxacin Oral Dosage	Equivalent Ciprofloxacin injection 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

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.

Table 3: Pediatric Dosage Guidelines

Infection	Dose (mg/kg	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)*	6 mg/kg to 10 mg/kg (maximum 400 mg per dose; not to be exceeded even in patients weighing more than 51 kg)	Every 8 hours	10–21 days*
Inhalational Anthrax (Post-Exposure)†	10 mg/kg (maximum 400 mg per dose)	Every 12 hours	60 days
Plague , † ‡	10 mg/kg (maximum 400 mg per dose)	Every 8 to 12 hours	14 days

*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).

†Begin drug administration as soon as possible after suspected or confirmed exposure.

‡Begin drug administration as soon as possible after suspected or confirmed exposure to Y. pestis.

Dosage Modifications in Patients with Renal Impairment

Ciprofloxacin Injection, USP 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
>30	See Usual Dosage
5–29	200–400 mg every 18–24 hours

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 and hepatic insufficiency, careful monitoring is suggested.
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).

4.3 Contraindications

Hypersensitivity

Ciprofloxacin is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterials, or any of the product components.

Tizanidine

Concomitant administration with tizanidine is contraindicated.

4.4 Special warnings and precautions for use

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

See full prescribing information for complete boxed warning.

- **Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:**
- **Tendinitis and tendon rupture**
- **Peripheral neuropathy**
- **Central nervous system effects**

Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones, including ciprofloxacin, in patients who experience any of these serious adverse reactions

- **Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.**
- **Because fluoroquinolones, including ciprofloxacin, have been associated with serious adverse reactions, reserve ciprofloxacin for use in patients who have no alternative treatment options for the following indications:**
- **Acute exacerbation of chronic bronchitis**
- **Acute sinusitis**

Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting ciprofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions.
Discontinue ciprofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including ciprofloxacin, in patients

who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Tendinitis and Tendon Rupture

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendons. Tendinitis or tendon rupture can occur, within hours or days of starting ciprofloxacin, or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors 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. Discontinue ciprofloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including ciprofloxacin, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture.

Peripheral Neuropathy

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of peripheral neuropathy. 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 fluoroquinolones, including ciprofloxacin. Symptoms may occur soon after initiation of ciprofloxacin and may be irreversible in some patients.

Discontinue ciprofloxacin immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness, or other alterations in sensations including light touch, pain, temperature, position sense and vibratory sensation, and/or motor strength in order to minimize the development of an irreversible condition. Avoid fluoroquinolones, including ciprofloxacin, in patients who have previously experienced peripheral neuropathy.

Central Nervous System Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations, or paranoia; depression, or self-injurious behavior such as attempted or completed suicide; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug, and institute appropriate care.

Central Nervous System Adverse Reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (pseudotumor cerebri), dizziness, and tremors. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. As with all

fluoroquinolones, use ciprofloxacin with caution in epileptic patients and patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (for example, severe cerebral arteriosclerosis, previous history of convulsion, reduced cerebral blood flow, altered brain structure, or stroke), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (for example, certain drug therapy, renal dysfunction). If seizures occur, discontinue ciprofloxacin, and institute appropriate care.

Exacerbation of Myasthenia Gravis
Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

Other Serious and Sometimes Fatal Adverse Reactions
Other serious and sometimes fatal adverse reactions, some due to hypersensitivity, and some due to uncertain etiology, have been reported 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.*

Discontinue ciprofloxacin immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy, including ciprofloxacin. 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, including intubation, as indicated.

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 ciprofloxacin for use only when there are no alternative antibacterial treatments available.

Hepatotoxicity
Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with ciprofloxacin. 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 ciprofloxacin.

Serious Adverse Reactions with Concomitant 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. 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 ciprofloxacin cannot be eliminated. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate.

Clostridioides difficile-Associated Diarrhea
Clostridioides difficile (C. 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 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.

Prolongation of the QT Interval
Some fluoroquinolones, including ciprofloxacin, 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 ciprofloxacin. Avoid ciprofloxacin 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.

Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Ciprofloxacin is indicated in pediatric patients (less than 18 years of age) only for cUTI, prevention of inhalational anthrax (post exposure), and plague. An increased incidence of adverse reactions compared to controls, including reactions related to joints and/or surrounding tissues, has been observed.

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.

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 ciprofloxacin, after sun or UV light exposure. Therefore, avoid excessive exposure to these sources of light. Discontinue ciprofloxacin if phototoxicity occurs.

Development of Drug Resistant Bacteria

Prescribing ciprofloxacin 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.

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

Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Co-administration of ciprofloxacin 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.

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. Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving ciprofloxacin. Hydrate patients well to prevent the formation of highly concentrated urine.

Periodic Assessment of Organ System Functions

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

Blood Glucose Disturbances

Fluoroquinolones, including ciprofloxacin, 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 ciprofloxacin, discontinue ciprofloxacin and initiate appropriate therapy immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration 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 co-administered drug.

Table 5: Drugs that are Affected by and Affecting ciprofloxacin

Drugs That are Affected by ciprofloxacin		
Drug(s)	**Recommendation**	**Comments**
Tizanidine	Contraindicated	Concomitant administration of tizanidine and ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine.
Theophylline	Avoid Use (Plasma Exposure Likely to be Increased and Prolonged)	Concurrent administration of ciprofloxacin with theophylline may result in increased risk of a patient developing central nervous system (CNS) or other adverse reactions. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate.
Drugs Known to Prolong QT Interval	Avoid Use	Ciprofloxacin may further prolong the QT interval in patients receiving drugs known to prolong the QT interval (for example, class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
Oral antidiabetic drugs	Use with caution Glucose-lowering effect potentiated	Hypoglycemia sometimes severe has been reported when ciprofloxacin and oral antidiabetic agents, mainly sulfonylureas (for example, glyburide, glimepiride), were co-administered, presumably by intensifying the action of the oral antidiabetic agent. Fatalities have been reported. Monitor blood glucose when ciprofloxacin is co-administered with oral antidiabetic drugs
Phenytoin	Use with caution Altered serum levels of phenytoin (increased and decreased)	To avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related adverse reactions upon ciprofloxacin discontinuation in patients receiving both agents, monitor phenytoin therapy, including phenytoin serum

		concentration during and shortly after co-administration of ciprofloxacin with phenytoin
Cyclosporine	Use with caution (transient elevations in serum creatinine)	Monitor renal function (in particular serum creatinine) when ciprofloxacin is co-administered with cyclosporine.
Anti-coagulant drugs	Use with caution (Increase in anticoagulant effect)	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. Monitor prothrombin time and INR frequently during and shortly after co-administration of ciprofloxacin with an oral anti-coagulant (for example, warfarin).
Methotrexate	Use with caution Inhibition of methotrexate renal tubular transport potentially leading to increased methotrexate plasma levels	Potential increase in the risk of methotrexate associated toxic reactions. Therefore, carefully monitor patients under methotrexate therapy when concomitant ciprofloxacin therapy is indicated.
Ropinirole	Use with caution	Monitoring for ropinirole-related adverse reactions and appropriate dose adjustment of ropinirole is recommended during and shortly after co-administration with ciprofloxacin
Clozapine	Use with caution	Careful monitoring of clozapine associated adverse reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.
NSAIDs	Use with caution	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 and in postmarketing.
Sildenafil	Use with caution Two-fold increase in exposure	Monitor for sildenafil toxicity
Duloxetine	Avoid Use Five-fold increase in duloxetine exposure	If unavoidable, monitor for duloxetine toxicity

Caffeine/Xanthine Derivatives	Use with caution Reduced clearance resulting in elevated levels and prolongation of serum half-life	Ciprofloxacin inhibits the formation of paraxanthine after caffeine administration (or pentoxifylline containing products). Monitor for xanthine toxicity and adjust dose as necessary.
Zolpidem	Avoid Use	Co-administration with ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended
Drug(s) Affecting Pharmacokinetics of ciprofloxacin		
Probenecid	Use with caution (interferes with renal tubular secretion of ciprofloxacin and increases ciprofloxacin serum levels)	Potentiation of ciprofloxacin toxicity may occur.

4.6 Fertility, pregnancy and breastfeeding

Risk Summary

Prolonged experience with ciprofloxacin in pregnant women over several decades, based on available published information from case reports, case control studies and observational studies on ciprofloxacin administered during pregnancy, have not identified any drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Oral administration of ciprofloxacin during organogenesis at doses up to 100 mg/kg to pregnant mice and rats, and up to 30 mg/kg to pregnant rabbits did not cause fetal malformations. These doses were up to 0.3, 0.6, and 0.4 times the maximum recommended clinical oral dose in mice, rats, and rabbits, respectively, based on body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Human Data

While available studies cannot definitively establish the absence of risk, published data from prospective observational studies over several decades have not established an association with ciprofloxacin use during pregnancy and major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available studies have methodological limitations including small sample size and some of them are not specific for ciprofloxacin. A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to ciprofloxacin and 68% first trimester exposures) during gestation. 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). 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. However, these small postmarketing epidemiology studies, of which most experience is from short term, first trimester exposure, are insufficient to evaluate the risk for less common defects or to permit reliable and definitive conclusions regarding the safety of ciprofloxacin in pregnant women and their developing fetuses.
Animal Data
Developmental toxicology studies have been performed with ciprofloxacin in rats, mice, and rabbits. In rats and mice, oral doses up to 100 mg/kg administered during organogenesis (Gestation Days, GD, 6-17) were not associated with adverse developmental outcomes, including embryo-fetal toxicity or malformations. In rats and mice, a 100 mg/kg dose is approximately 0.6 and 0.3 times the maximum daily human oral dose (1500 mg/day) based upon body surface area, respectively. In a series of rabbit developmental toxicology studies, does received oral or intravenous ciprofloxacin for 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 anti-bacterials manifested by reduced maternal food consumption and weight loss, that can lead to embryo-fetal 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.

Breast-feeding
Risk Summary
Published literature reports that ciprofloxacin is present in human milk following intravenous and oral administration. There is no information regarding effects of ciprofloxacin 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 for most indications a lactating woman may consider pumping and discarding breast milk during treatment with ciprofloxacin and an additional two days (five half-lives) after the last dose. Alternatively, advise a woman that breastfeeding is not recommended during treatment with ciprofloxacin 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 ciprofloxacin may be acceptable. The developmental and

health benefits of breastfeeding should be considered along with the mother's clinical need for ciprofloxacin and any potential adverse effects on the breastfed child from ciprofloxacin 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).

4.7 Effects on ability to drive and use machines

Ciprofloxacin can cause dizziness and light-headedness. Do not drive, operate machinery, or do other activities that require mental alertness or coordination.

4.8 Undesirable effects

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
- Tendinitis and Tendon Rupture
- Peripheral Neuropathy
- Central Nervous System Effects
- Exacerbation of Myasthenia Gravis
- Other Serious and Sometimes Fatal Adverse Reactions
- Hypersensitivity Reactions
- Risk of Aortic Aneurysm and Dissection
- Hepatotoxicity
- Serious Adverse Reactions with Concomitant Theophylline
- Clostridioides difficile-Associated Diarrhea
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Photosensitivity/Phototoxicity
- Development of Drug Resistant Bacteria

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 ciprofloxacin, 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%).

In clinical trials the following adverse reactions were reported in greater than 1% of patients treated with intravenous ciprofloxacin: nausea, diarrhea, central nervous system disturbance, local intravenous site reactions, liver function tests abnormal, eosinophilia, headache, restlessness, and rash. Local intravenous site reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions that resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Table 6: Medically Important Adverse Reactions That Occurred in less than 1% Ciprofloxacin Patients

System Organ Class	Adverse Reactions
Body as a Whole	Abdominal Pain/Discomfort Pain
Cardiovascular	Cardiopulmonary Arrest Myocardial Infarction Tachycardia Syncope Hypertension Angina Pectoris Vasodilation
Central Nervous System	Restlessness Seizures (including Status Epilepticus) Paranoia Psychosis (toxic) Depression (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughts and attempted or completed suicide) Phobia Depersonalization Manic Reaction Unresponsiveness Ataxia Hallucinations Dizziness Paresthesia Tremor Insomnia Nightmares Irritability Malaise Abnormal Gait Migraine
Gastrointestinal	Ileus Gastrointestinal Bleeding Pancreatitis Hepatic Necrosis Intestinal Perforation Dyspepsia Constipation Oral Ulceration Mouth Dryness Anorexia Flatulence Hepatitis
Hemic/Lymphatic	Agranulocytosis Prolongation of Prothrombin Time Petechia
Metabolic/Nutritional	Hyperglycemia

	Hypoglycemia
Musculoskeletal	Arthralgia Joint Joint Stiffness Muscle Weakness
Renal/Urogenital	Renal Failure Interstitial Nephritis Hemorrhagic Cystitis Renal Calculi Frequent Urination Gynecomastia Crystalluria Cylindruria Hematuria Albuminuria
Respiratory	Respiratory Arrest Dyspnea Laryngeal Edema Hemoptysis Bronchospasm
Skin/Hypersensitivity	Allergic Reactions Anaphylactic Reactions including life-threatening anaphylactic shock Erythema Multiforme/Stevens-Johnson Syndrome Exfoliative Dermatitis Toxic Epidermal Necrolysis Vasculitis Angioedema Extremities Purpura Fever Pruritus Urticaria Increased Perspiration Erythema Nodosum Thrombophlebitis Burning Photosensitivity/Phototoxicity Reaction
Special Senses	Decreased Visual Acuity Blurred Vision Disturbed Vision (diplopia, chromatopsia, and photopsia) Anosmia Hearing Loss Tinnitus Nystagmus 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 (Intravenous and Intravenous/Oral sequential) with intravenous beta-lactam control antibiotics, the CNS adverse reaction profile of ciprofloxacin was comparable to that of 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 7).

Table 7: Musculoskeletal Adverse Reactions as Assessed by the IPSC

	Ciprofloxacin	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 to 24 months	1/36 (2.8%)	0/41
2 years to <6 years	5/124 (4%)	3/118 (2.5%)
6 years to <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[2]	(-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 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 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 events 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 ciprofloxacin 10 mg/kg/dose every 8 hours for one week followed by ciprofloxacin 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 ciprofloxacin 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.

Postmarketing Experience
The following adverse reactions have been reported from worldwide marketing experience with fluoroquinolones, including ciprofloxacin. 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 8).

Table 8: Postmarketing Reports of Adverse Drug Reactions

System Organ Class	Adverse Reactions
Cardiovascular	QT prolongation Torsade de Pointes Vasculitis and ventricular arrhythmia
Central Nervous System	Hypertonia Myasthenia Exacerbation of myasthenia gravis Peripheral neuropathy Polyneuropathy Twitching
Gastrointestinal	Pseudomembranous colitis

Hemic/Lymphatic	Pancytopenia (life threatening or fatal outcome) Methemoglobinemia
Hepatobiliary	Hepatic failure (including fatal cases)
Infections and Infestations	Candidiasis (oral, gastrointestinal, vaginal)
Investigations	Prothrombin time prolongation or decrease Cholesterol elevation (serum) Potassium elevation (serum)
Musculoskeletal	Myalgia Myoclonus Tendinitis Tendon rupture
Psychiatric Disorders	Agitation Confusion Delirium
Skin/Hypersensitivity	Acute generalize exanthematous pustulosis (AGEP) Fixed eruption Serum sickness-like reaction
Special Senses	Anosmia Hyperesthesia Hypesthesia Nystagmus Taste loss

Adverse Laboratory Changes
Changes in laboratory parameters while on ciprofloxacin therapy 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 were: decreased leukocyte count, elevated atypical lymphocyte count, immature WBCs, elevated serum calcium, elevation of serum gamma-glutamyl transpeptidase (gGT), decreased BUN, decreased uric acid, decreased total serum protein, decreased serum albumin, decreased serum potassium, elevated serum potassium, elevated serum cholesterol. Other changes occurring 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.

4.9 Overdose
In the event of acute overdosage, reversible renal toxicity has been reported in some cases. Observe the patient carefully and give supportive treatment, including monitoring of renal function, urinary pH and acidify, if required, to prevent crystalluria. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (less than 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 mg/kg and 300 mg/kg.

5. Pharmaceutical properties

5.1 Pharmacodynamic properties
Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents.

5.2 Pharmacokinetic properties

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 (Table 9).

Table 9: Steady-state Ciprofloxacin Serum Concentrations (mcg/mL) After 60-minute INTRAVENOUS Infusions every 12 hours.

	Time after starting the infusion					
Dose	**30 minutes**	**1 hour**	**3 hour**	**6 hour**	**8 hour**	**12 hour**
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 mg to 400 mg administered intravenously. Comparison of the pharmacokinetic parameters following the 1st and 5th intravenous dose on an every 12 hour 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 intravenous dose results in a Cmax similar to that observed with a 750-mg oral dose (Table 10). 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.

Table 10: 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
$AUC_{(0\text{-}24h),ss}$ (mcg.hr/mL)	27.4*	25.4*	31.6*	32.9*
C_{max} (mcg/mL)	2.97	4.56	3.59	4.07

*$AUC_{0\text{-}12h}$ x2

** $AUC_{0\text{-}8h}$ x3

Distribution

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

Metabolism

After intravenous administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The metabolites have antimicrobial activity, but are less active than unchanged. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration 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 co-administered drug.

Excretion

The serum elimination half-life is approximately 5–6 hours and the total clearance is around 35 L/hr. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200-mg intravenous dose, concentrations in the urine usually exceed 200 mcg/mL 0–2 hours after dosing and are generally greater than 15 mcg/mL 8–12 hours after dosing. Following a 400 mg intravenous dose, urine concentrations generally exceed 400 mcg/mL 0–2 hours after dosing and are usually greater than 30 mcg/mL 8–12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after intravenous dosing, only a small amount of the administered dose (<less than 1%) is recovered from the bile as unchanged drug. Approximately 15% of an intravenous dose is recovered from the feces within 5 days after dosing.

Specific Populations

Elderly

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 (older than 65 years) as compared to young adults. Although the C 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.

Specific Populations

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Renal Impairment

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required.

Hepatic Impairment

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

Pediatrics

Table 11 summarizes pharmacokinetic parameters in pediatric patients aged less than 1 to less than 12 years of age receiving intravenous treatment.

Table 11: Estimated $AUC_{0\text{-}24,ss}$ and $C_{max,ss}$, for Intravenous Treatment (1-h infusion) in Pediatric Patients following a Multiple Dosing Regimen of 10 mg/kg , Three Times Daily

Age	$AUC_{0-24,ss}$ (mg h/L)	$C_{max,ss}$ (mg/L)
Less than 1 year	30.9*	2.8*
1 to less than 2 years	27.8*	3.6*
2 to less than 6 years	28.9*	2.7*
6 to less than 12 years	20.4*	2.0*

*3 x $AUC_{0-8,ss}$

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 hours–5 hours, and the bioavailability of the oral suspension is approximately 60%.

Drug-Drug Interactions

Metronidazole

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

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 twice a day for 3 days). Concomitant administration of tizanidine and ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine.

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 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 ciprofloxacin.

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 reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil

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

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 500 mg ciprofloxacin 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 ciprofloxacin and an increase in adverse reactions related to lidocaine may occur upon concomitant administration.

5.3 Preclinical safety data

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 V79 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- times 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 to 32 weeks in mice treated concomitantly with UVA and other quinolones.

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.

Animal Toxicology and/or Pharmacology

Ciprofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested.

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.

6. Pharmaceutical particulars

6.1 List of excipients
Sodium Chloride USP
Edetate Disodium USP
Lactic Acid USP
Sodium Hydroxide USP
Water for Injection USP

6.2 Incompatibilities
Not Applicable

6.3 Shelf life
3 years

6.4 Special precautions for storage
Store at a temperature not exceeding 30°C. Do not freeze. Protect from light.

6.5 Nature and content of container

100 ml Sterile, Non Pyrogenic, Isotonic Single dose LDPE bottle. One such bottle is packed in a unit carton along with a leaflet.

6.6 Special precautions for disposal and other handling
Not Applicable

7. Marketing authorization holder

UNIQUE PHARMACEUTICAL LABORATORIES
(A Division of J.B. Chemicals & Pharmaceuticals Ltd.)
Neelam center, B Wing, 4th floor, Hind cycle road,
Worli, Mumbai 400 030, INDIA

8. Marketing Authorization Number
05124/3082/NMR/2017

9. Date of First Authorization/Renewal of the Authorization
20/4/2020

10. Date of revision of the text
27/07/2023