For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

SUMMARY OF PRODUCT CHARACTERISTICS

CIPROFLOXACIN TABLETS USP 500 MG

1. NAME OF THE MEDICINAL PRODUCT

CIPROFLOXACIN TABLETS USP 500 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:
Ciprofloxacin Hydrochloride USP
Equivalent to Ciprofloxacin.....500 mg

3. PHARMACEUTICAL FORM

Film coated Tablets.
Product description/visual appearance as stated in the FPP specifications: White colored, biconvex, capsule shaped, film coated tablets, plain on both sides, free from cracks, mottling, and chips in the tablet surface.

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 *Enterbacter 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*.

Infectious Diarrhea

Ciprofloxacin 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.

Typhoid Fever (Enteric Fever)

Ciprofloxacin 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.

Uncomplicated Cervical and Urethral Gonorrhea

Ciprofloxacin is indicated in adult patients for treatment of uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae.*

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*.

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 pneumoniae* 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.*

Acute Uncomplicated Cystitis

Ciprofloxacin is indicated in adult female patients for treatment of acute uncomplicated cystitis caused by *Escherichia coli* or *Staphylococcus saprophyticus.*
Because fluoroquinolones, including Ciprofloxacin, have been associated with serious adverse reactions and for some patients acute uncomplicated cystitis is self-limiting, reserve Ciprofloxacin for treatment of acute uncomplicated cystitis in patients who have no alternative treatment options.

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 Tablets should be administered orally as 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.
Ciprofloxacin Tablets may be administered to adult patients when clinically indicated at the discretion of the physician.

Table 1: Adult Dosage Guidelines

Infection	Dose	Frequency	Usual Duration[1]
Skin and Skin Structure	500–750 mg	every 12 hours	7-14 days
Bone and Joint	500–750 mg	every 12 hours	4 to 8 weeks
Complicated Intra-Abdominal[2]	500 mg	Every 12 hours	7-14 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]	500mg	every 12 hours	60 days

Plague[3]	500–750 mg	every 12 hours	14 days
Chronic Bacterial Prostatitis	500mg	every 12 hours	28 days
Lower Respiratory Tract Infections	500–750 mg	every 12 hours	7-14 days
Urinary Tract Infections	250–500 mg	every 12 hours	7-14 days
Acute Uncomplicated Cystitis	250 mg	every 12 hours	3 days
Acute Sinusitis	400mg	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 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 IV may be switched to Ciprofloxacin Tabletwhen clinically indicated at the discretion of the physician.

Table 2. Equivalent AUC Dosing Regimens

Ciprofloxacin Oral Dosage	Equivalent Ciprofloxacin IV Dosage
250mg Tablet every 12 hours	200mg intravenous every 12 hours
500mg Tablet every 12 hours	400mg intravenous every 12 hours
750mg Tablet every 12 hours	400mg 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. Ciprofloxacin should be administered as described inTable 3.

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)[1]	10 mg/kg to 20mg/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	15mg/kg (maximum	Every 12 hours	60 days

(Post-Exposure)	500mg per dose)		
Plague[2,3]	15mg/kg (maximum 500mg per dose)	Every 8 to 12 hours	10-21 days

[1] The total duration of therapy for cUTI and pyelonephritis in the clinical trial was determined bythe 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*.

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 toestimate creatinine clearance:

Men – Creatinine clearance (mL/min) = Weight (kg) x (140-age)

$$\frac{}{72 \times \text{serum creatinine (mg/dL)}}$$

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 forpediatric patients with moderate to severe renal insufficiency (that is, creatinine clearance of < 50 mL/min/1.73m^2).

Important Administration Instruction
With Multivalent Cations

Administer Ciprofloxacin at least 2 hours before or 6 hours after magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate) or sucralfate; 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 Ciprofloxacin with dairy products (like milk or yogurt) or calcium-fortified juices alone should be avoided since decreased absorption is possible; however,Ciprofloxacin may be taken with a meal that contains these products.

Hydration of Patients Receiving Ciprofloxacin

Assure adequate hydration of patients receiving Ciprofloxacin to prevent the formation of highlyconcentrated urine. Crystalluria has been reported with quinolones.
Instruct the patient of the appropriate Ciprofloxacin administration.

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

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 factor, 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, 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 complete 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 (pscudotumor 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 ventilator 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 measure 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.

Hepatotoxicity

Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, andfatal 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.

***Clostridium difficile*-Associated Diarrhea**

Clostridium 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 surroundingtissues, 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 tablets in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increasesthe 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.

Interference with Timely Diagnosis of Syphilis

Ciprofloxacin has not been shown to be effective in the treatment of syphilis. Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. 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 Ciprofloxacin treatment.

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 preventthe formation of highly concentrated urine.

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. Severecases 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 initiateappropriate therapy immediately.

Patient Counselling Information

Serious Adverse Reactions

Advise patients to stop taking Ciprofloxacin if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug.

Inform patients of the following serious adverse reactions that have been associated with Ciprofloxacin or other fluoroquinolone use:

Disabling and potentially irreversible serious adverse reactions that may occur together: Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of Ciprofloxacin and may occur together in the same patient. Inform patients to stop taking Ciprofloxacin 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 Ciprofloxacin 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 Ciprofloxacin 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 Ciprofloxacin 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 Ciprofloxacin. 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.

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 patientsto 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.

Tizanidine: Instruct patients not to use ciprofloxacin if they are already taking tizanidine. Ciprofloxacin increases the effects of tizanidine.

Theophylline: Inform patients that Ciprofloxacin 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 Ciprofloxacin 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 Ciprofloxacin and consult a physician.

Antibacterial Resistance

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

Administration with Food, Fluids, and Concomitant Medications

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

Inform patients to drink fluids liberally while taking Ciprofloxacin to avoid formation of highlyconcentrated urine and crystal formation in the urine.

Inform patients that antacids containing magnesium, or aluminum, as well as sucralfate, metalcations such as iron, and multivitamin preparations with zinc or didanosine should be taken at

least two hours before or six hours after Ciprofloxacin administration. Ciprofloxacin 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, Ciprofloxacin may be taken with a meal that contains these products.

Drug Interactions Oral Antidiabetic Agents

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

Anthrax and Plague Studies

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

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 resultsin increased plasma concentrations of these drugs and could lead to clinically significant adverseevents of the co-administered drug.

Table 8. 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 iscontraindicated 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 withtheophylline may result inincreased 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 QTInterval	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 (foe example, glycuride, glimepiride), were co-administered, presumablyby 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 withphenytoin.
Cyclosporine	Use with caution (transient	Monitor renal function (in

	elevations in serumcreatinine)	particular serum creatinine) when ciprofloxacin is co-administered with cyclosporine.
Anti-coagulant drugs	Use with caution (Increase inanticoagulant 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 acetylsalicylic 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 inexposure	Monitor for sildenafiltoxicity.
Duloxetine	Avoid use Five-fold increase induloxetine exposure	If unavoidable, monitor for duloxetine toxicity.
Caffeine / XanthineDerivatives	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		

Antacids, Sucralfate,Multivitamins and Other Products ContainingMultivalent Cations (magnesium/aluminum antacids; polymericphosphate binders (for example, sevelamer, lanthanum carbonate); sucralfate; didanosine chewable/ buffered tablets or pediatric powder; other highly	Ciprofloxacin should be taken at least two hours before or six hours after multivalent cation containing products administration.	Decrease Ciprofloxacin absorption, resulting in lower serum and urine levels.

buffered drugs; or products containing calcium, iron, or zinc and dairy products)		
Probenecid	Use with caution (interferes with renal tubular secretion of Ciprofloxacin and increases Ciprofloxacin serum levels)	Potentiation of Ciprofloxacintoxicity may occur.

4.6. Fertility, pregnancy and lactationPregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother. An expert review of published data on experiences with ciprofloxacin use during pregnancy by TERIS-the Teratogen Information System-concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk (quantity and quality of data = fair), but the data are insufficient to state that there is no risk.

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.

As reported in pre-clinical experience, after intravenous administration of doses up to 20 mg/ kg(approximately 0.3-times the highest recommended therapeutic dose based upon body surfacearea), no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. **Nursing Mothers**

Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential risk of serious adverse reactions (including articular damage) in infants nursing from mothers taking Ciprofloxacin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

4.7. Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8. Undesirable effects

Following adverse events are reported more frequently in clinical experience:

Nausea, diarrhoea, liver function tests abnormal, vomiting, rash, central nervous system disturbance, local intravenous site reactions, eosinophilia, headache, restlessness. 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. Subsequentintravenous administration is not contraindicated unless the reactions recur or worsen.

Medically Important Adverse Reactions that Occurred in clinical experience:

System Organ Class	**Adverse Reactions**
Body as a Whole	Abdominal Pain / Discomfort Pain
Cardiovascular	Cardiopulmonary ArrestMyocardial 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 Depersonalizati onManic Reactions Unresponsivene ssAtaxia Hallucinations Dizziness Paresthesia Tremor Insomnia Nightmares Irritability Malaise Abnormal GaitMigraine

Gastrointestinal	Ileus Gastrointestinal BleedingPancreatitis Hepatic Necrosis Intestinal Perforation Dyspepsia Constipation Oral Ulceration Mouth Dryness Anorexia

	Flatulence Hepatitis
Hemic / Lymphatic	Agranulocytosis Prolongation of Prothrombin TimePetechia
Metabolic / Nutritional	Hyperglycemia Hypoglycemia
Musculoskeletal	Arthralgia Joint Stiffness Muscle Weakness
Renal / Urogenital	Renal Failure Interstitial Nephritis Hemorrhagic CystitisRenal Calculi Frequent Urination Gynecomastia Crystalluria Cylindruria Hematuria Albuminuria
Respiratory	Respiratory ArrestDyspnea Laryngeal Edema Hemoptysis Bronchospasm

Skin / Hypersensitivity	Allergic Reactions Anaphylactic Reactions including life-threateninganaphylactic shock Erythema Multiforme / Stevens-Johnson SyndromeExfoliative Dermatitis Toxic Epidermal NecrolysisVasculitis Angioede ma Extremitie s Purpura Fever Pruritus Urticaria Increased Perspiration Erythema Nodosum Thrombophlebitis Burning Photosensitivity / Phototoxicity Reaction
Special Senses	Decreased Visual AcuityBlurred 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.

Pediatric Patients

Musculoskeletal adverse reactions: 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)

Neurological adverse reactions dizziness, nervousness, insomnia, and somnolence.

Other adverse reactions includes diarrhoea, vomiting, abdominal pain, dyspepsia, nausea, fever, asthma, and rash.

Post marketing Experience

The following adverse reactions have been reported from worldwide marketing experience with fluoroquinolones, including Ciprofloxacin.

System Organ Class	**Adverse Reactions**
Cardiovascular	QT prolongation Torsade de Pointes Vasculitis and ventricular arrhythmia
Central Nervous System	Hypertoni a Myasthen ia Exacerbation of myasthenia gravisPeripheral neuropathy Polyneuropathy Twitching
Eye disorder	Nystagmus
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 Myoclon us Tendinitis Tendon rupture
Psychiatric Disorders	Agitation Confusion Delirium
Skin / Hypersensitivity	Acute generalize exanthematous pustulosis

	(AGEP) Fixed eruption Serum sickness-like reaction
Special Senses	Anosmia Hyperesthes ia Hyperesthes ia Taste loss

Adverse Laboratory Changes
Changes in laboratory parameters while on Ciprofloxacin 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 havebeen 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.

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.

5. PHARMACOLOGICAL PROPERTIES
5.1. Pharmacodynamic properties
Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents.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 invitro and in clinical infections.

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 parainfluenzaeKlebsiella pneumoniae Moraxella catarrhalis Morganella morganii Neisseria gonorrhoeae Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosaSalmonella typhi
Serratia marcescensShigella boydii Shigella dysenteriaeShigella 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 (≤1 mcg/mL). However, the efficacy of ciprofloxacin in treating clinical infections due to these bacteria has not been established in adequate and well-controlled clinical trials.

Gram-positive bacteria

Staphylococcus haemolyticus (methicillin-susceptible isolates only)*Staphylococcus hominis* (methicillin-susceptible isolates only)

Gram-negative bacteria

Acinetobacter lwoffi
Aeromonas hydrophila
Edwardsiella tarda
Enterobacter aerogenesKlebsiella oxytoca Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis
Vibrio cholerae
Vibrio parahaemolyticusVibrio vulnificus Yersinia enterocolitica

5.2. Pharmacokinetic properties

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 (Cmax) and area under the curve (AUC) are shown in the chart for the 250 mg to 1000 mg dose range (Table below).

Ciprofloxacin C_{max} and AUC Following Administration of Single Doses of Ciprofloxacin Tablets.

Dose (mg)	C_{max} (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 Ciprofloxacin given over 60 minutes every 12 hours. A 750 mg oral dose given every 12 hours has been shown to produce an AUC at steady-

state equivalent to that produced by an intravenous infusion of 400 mg given over 60 minutes every 8 hours. A 750 mg oral dose results in a Cmax similar to that observed with a 400 mg intravenous dose. A 250 mg oral dose given every 12 hours produces an AUC equivalent to that produced by an infusion of 200 mg Ciprofloxacin given every 12 hours (Table below).

Steady-state Pharmacokinetic Parameters Following Multiple Oral and Intravenous Doses

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 (mcg·hr/mL)	13.7[1]	12.7[1]	31.6[2]	32.9[3]
C_{max} (mcg/mL)	2.97	4.56	3.59	4.07

[1]. AUC 0-12h

[2]. AUC 24h = AUC 0-12h x 2

[3]. AUC 24h = AUC 0-8h x

3Food

When Ciprofloxacin 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. The overall absorption of Ciprofloxacin Tablet, however, is not substantially affected. The pharmacokinetics of ciprofloxacin given as the suspension are also not affected by food. Avoid concomitant administration of Ciprofloxacin with dairy products (like milk or yogurt) or calcium-fortified juices alone since decreased absorption is possible; however, Ciprofloxacin may be taken with a meal that contains these products.

Distribution

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

After oral administration, ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genitaltissue 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

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. 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 in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. After a 250 mg oral dose, urine concentrations of ciprofloxacin usually exceed 200mcg/ mL during the first two hours and are approximately 30 mcg/mL at 8 to 12 hours after dosing.

The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the

normal glomerular filtration rate of 120 mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Co-administration of probenecid with ciprofloxacin results in about a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its concentration in the systemic circulation.

Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1% to 2% of the dose is recovered from the bile in the form of metabolites. Approximately 20% to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or trans intestinal elimination.

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 Cmax 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.

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

The pharmacokinetics parameters are within the range as 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

Antacids

Concurrent administration of antacids containing magnesium hydroxide or aluminum hydroxidemay reduce the bioavailability of ciprofloxacin by as much as 90%.

Histamine H2-receptor antagonists

Histamine H2-receptor antagonists appear to have no significant effect on the bioavailability ofciprofloxacin.

Metronidazole

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

Tizanidine

Concomitant administration of tizanidine and Ciprofloxacin is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine.

Ropinirole

The mean C_{max} and mean AUC of ropinirole increases after concomitant administration of ropinirole and ciprofloxacin. 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 Ciprofloxacin with clozapine, serum concentrations of clozapine and N-desmethylclozapine increases. 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 sildenafil with Ciprofloxacin, the mean Cmax and mean AUC of sildenafil increases 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 Cmax of duloxetine.

Lidocaine

Concomitant use of lidocaine with ciprofloxacin twice daily results in an increase of lidocaine Cmax and AUC. 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.

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 thebioavailability of ciprofloxacin.

Omeprazole

When ciprofloxacin is administered concomitantly with omeprazole, the mean AUC and Cmaxof ciprofloxacin reduces.

The clinical significance of this interaction has not been determined.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies in rats and mice report 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 2.5times the highest recommended therapeutic dose based upon body surface area, respectively).

The clinical significance of these findings to humans is unknown.

Fertility studies in rats at oral doses of ciprofloxacin up to 100 mg/kg (approximately 0.7-times the highest recommended therapeutic dose based upon body surface area) reveals no evidence of impairment.

Animal Toxicology and/or Pharmacology

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

Crystalluria, sometimes associated with secondary nephropathy, occurs in laboratory animals dosed with ciprofloxacin. This is primarily related to the reduced solubility of ciprofloxacinunder alkaline conditions, which predominate in the urine of test animals; in man, crystalluria is rare since human urine is typically acidic.
Studies in animals also reported that 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. 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 as reported in pre-clinical experience.
Ocular toxicity seen with some related drugs has not been observed in ciprofloxacin-treated animals.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Ingredient	Specification
Pregelatinised Starch	NF
Microcrystalline Cellulose	NF
Colloidal Silicon Dioxide	NF
Crospovidone	NF
Magnesium Stearate	NF
Opadry White Y-1-7000	IH
Polyethylene Glycol 4000	NF
Purified Water	USP

Qualitative composition of Opadry White Y-1-7000

%w/w	Ingredients/Compendial Reference	Grade/ Dye Strength	E Number	CFR Reference	CI Number
62.500	HPMC2910/ HYPROMELLOSE(USP, PhEur, JP, FCC, ChP, GB)	5 mPas	E464	172.874	
31.250	TITANIUM DIOXIDE (USP, PhEur, JP, JSFA,FCC,ChP, GB)	-	E171	73.575,73.1 575,73.2575	77891

6.250	MACROGOL/PEG (NF, FCC, PhEur, JECFA, JP)	MW 400	E1521	172.820	-

6.2. Incompatibilities
Not Applicable

6.3. Shelf life
3 years

6.4. Special precautions for storage

Do not store above 30°C. Protect from light.

6.5. Nature and contents of container
HDPE bottle of 100 tablets along with leaflet.

6.6. Special precautions for disposal and other handling
Not Applicable

7. MARKETING AUTHORISATION HOLDER

Unique Pharmaceutical Laboratories
(A Div. of J. B. Chemicals & Pharmaceuticals Ltd.)
Neelam centre, '8' Wing, 4 th Floor, Hind Cycle Road,
Worli, Mumbai-400 030, **India.**

8. MARKETING AUTHORISATION NUMBER(S)

TAN 21 HM 0299

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

20th August, 2021

10. DATE OF REVISION OF THE TEXT
NA