Cipra (Ciprofloxacin)

سپرا ٹیبلیٹ

(سپروفلاکسان)

250mg & 500mg Tablets

۲۵۰ ملی گرام اور ۵۰۰ ملی گرام ٹیبلیٹ

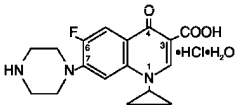
WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

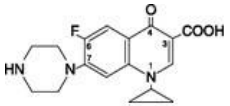
• Fluoroquinolones, including CIPRA, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together [see Warnings and Precautions including:
o Tendinitis and tendon rupture [see Warnings and Precautions
o Peripheral neuropathy [see Warnings and Precautions
o Central nervous system effects [see Warnings and Precautions
• Discontinue CIPRA immediately and avoid the use of fluoroquinolones, including CIPRA, in patients who experience any of these serious adverse reactions [see Warnings and Precautions. Fluoroquinolones, including CIPRA, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid CIPRA in patients with known history of myasthenia gravis [see Warnings and Precautions.
• Because fluoroquinolones, including CIPRA, have been associated with serious adverse reactions [see Warnings and Precautions, reserve CIPRA for use in patients who have no alternative treatment options for the following indications:
o Acute exacerbation of chronic bronchitis [see Indications and Usage
o Acute uncomplicated cystitis [see Indications and Usage
o Acute sinusitis [see Indications and Usage

1. DESCRIPTION

CIPRA (CIPRAfloxacin hydrochloride) Tablets and CIPRA (CIPRAfloxacin) is synthetic antimicrobial agents for oral administration. CIPRAfloxacin hydrochloride, USP, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3quinolinecarboxylic acid. It is a faintly yellowish to light yellow crystalline substance with a molecular weight of 385.8. Its empirical formula is $C_{17}H_{18}FN_3O_3$•HCl•H2O and its chemical structure is as follows:



CIPRAfloxacin is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is C17H18FN3O3 and its molecular weight is 331.4. It is a faintly yellowish to light yellow crystalline substance and its chemical structure is as follows:



CIPRA film-coated tablets are available in 250 mg and 500 mg (CIPRAfloxacin equivalent) strengths.

Composition:
Cipra Tablet 250:
Each film coated tablet contains:
CIPRAfloxacin as HCl 250 mg.
(USP Specification)

Cipra Tablet 500:
Each film coated tablet contains:
CIPRAfloxacin as HCl 500 mg.
(USP Specification)

2 INDICATIONS AND USAGE

2.1 Skin and Skin Structure Infections

CIPRA 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,* methicillinsusceptible *Staphylococcus aureus,* methicillin-susceptible *Staphylococcus epidermidis,* or *Streptococcus pyogenes.*

2.2 Bone and Joint Infections

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

2.3 Complicated Intra-Abdominal Infections

CIPRA 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.*

2.4 Infectious Diarrhea

CIPRA 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.

2.5 Typhoid Fever (Enteric Fever)

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

2.6 Uncomplicated Cervical and Urethral Gonorrhea

CIPRA is indicated in adult patients for treatment of uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae [see Warnings and Precautions.*

2.7 Inhalational Anthrax (Post-Exposure)

CIPRA is indicated in adults and pediatric patients from birth to 17 years of age for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

CIPRAfloxacin serum concentrations achieved in humans served as a surrogate endpoint reasonably likely to predict clinical benefit and provided the initial basis for approval of this indication.1 Supportive clinical information for CIPRAfloxacin for anthrax post-exposure prophylaxis was obtained during the anthrax bioterror attacks of October 2001 [see Clinical Studies.]

2.8 Plague

CIPRA 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 CIPRAfloxacin could not be conducted in humans with plague for feasibility reasons. Therefore this indication is based on an efficacy study conducted in animals only [see Clinical Studies.

2.9 Chronic Bacterial Prostatitis

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

2.10 Lower Respiratory Tract Infections

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

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

Because fluoroquinolones, including CIPRA, have been associated with serious adverse reactions [see Warnings and Precautions (5.1–5.15)] and for some patients AECB is self-limiting, reserve CIPRA for treatment of AECB in patients who have no alternative treatment options.

2.11 Urinary Tract Infections

Urinary Tract Infections in Adults

CIPRA 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

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

Because fluoroquinolones, including CIPRA, have been associated with serious adverse reactions [see Warnings and Precautions (5.1-5.15)] and for some patients acute uncomplicated cystitis is self-limiting, reserve CIPRA for treatment of acute uncomplicated cystitis in patients who have no alternative treatment options.

Complicated Urinary Tract Infection and Pyelonephritis in Pediatric Patients

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

Although effective in clinical trials, CIPRA 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. CIPRA, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals [see Warnings and Precautions (5.12), Adverse Reactions (6.1), Use in Specific Populations (8.4) and Nonclinical Toxicology.

2.12 Acute Sinusitis

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

Because fluoroquinolones, including CIPRA, have been associated with serious adverse reactions [see Warnings and Precautions (5.1-5.15)] and for some patients acute sinusitis is self-limiting, reserve CIPRA for treatment of acute sinusitis in patients who have no alternative treatment options.

2.13 Usage

To reduce the development of drug-resistant bacteria and maintain the effectiveness of CIPRA and other antibacterial drugs, CIPRA 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 CIPRAfloxacin. Therapy with CIPRA 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 CIPRAfloxacin. 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.

3 DOSAGE AND ADMINISTRATION

CIPRA Tablets should be administered orally as described in the appropriate Dosage Guidelines tables.

3.1 Dosage in Adults

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

Table 1: Adult Dosage Guidelines

Infection	Dose	Frequency	Usual Durations1
Skin and Skin Structure	500–750 mg	every 12 hours	7 to 14 days
Bone and Joint	500–750 mg	every 12 hours	4 to 8 weeks
Complicated Intra–Abdominal2	500 mg	every 12 hours	7 to 14 days
Infectious Diarrhea	500 mg	every 12 hours	5 to 7 days
Typhoid Fever	500 mg	every 12 hours	10 days
Uncomplicated Urethral and Cervical Gonococcal Infections	250 mg	single dose	single dose
Inhalational anthrax (post-exposure)3	500 mg	every 12 hours	60 days
Plague 3	500–750 mg	every 12 hours	14 days
Chronic Bacterial Prostatitis	500 mg	every 12 hours	28 days
Lower Respiratory Tract Infections	500–750 mg	every 12 hours	7 to 14 days
Urinary Tract Infections	250–500 mg	every 12 hours	7 to 14 days
Acute Uncomplicated Cystitis	250 mg	every 12 hours	3 days
Acute Sinusitis	500 mg	every 12 hours	10 days

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

Table 2: Equivalent AUC Dosing Regimens

CIPRA Oral Dosage
250 mg Tablet every 12 hours
500 mg Tablet every 12 hours

3.2 Dosage in Pediatric Patients

Dosing and initial route of therapy (that is, IV or oral) for cUTI or pyelonephritis should be determined by the severity of the infection. CIPRA should be administered as described in Table 3.

Table 3: Pediatric Dosage Guidelines

Infection	Dose	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis (patients from 1 to 17 years of age)	10 mg/kg to 20 mg/kg (maximum 750 mg per dose; not to be exceeded even in patients weighing more than 51 kg)	Every 12 hours	10–21 days1
Inhalational Anthrax (Post- Exposure)2	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	60 days
Plague2,3	15 mg/kg (maximum 500 mg 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 by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).
2. Begin drug administration as soon as possible after suspected or confirmed exposure.
3. Begin drug administration as soon as possible after suspected or confirmed exposure to Y. pestis.

3.3 Dosage Modifications in Patients with Renal Impairment

CIPRAfloxacin 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 every12 hours
5–29	250–500 mg every 18 hours
Patients on hemodialysis or Peritoneal dialysis	250–500 mg every 24 hours (after dialysis)

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

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

Women -0.85 x the value calculated for men.

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

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

Pediatric patients with moderate to severe renal insufficiency were excluded from the clinical trial of cUTI and pyelonephritis. No information is available on dosing adjustments necessary for pediatric patients with moderate to severe renal insufficiency (that is, creatinine clearance of < 50 mL/min/1.73m2).

4 CONTRAINDICATIONS

4.1 Hypersensitivity

CIPRA is contraindicated in persons with a history of hypersensitivity to CIPRAfloxacin, any member of the quinolone class of antibacterials, or any of the product components [see Warnings and Precautions].

4.2 Tizanidine

Concomitant administration with tizanidine is contraindicated [see Drug Interactions.

5. WARNINGS AND PRECAUTIONS

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

Fluoroquinolones, including CIPRA, 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 CIPRA. Patients of any age or without pre-existing risk factors have experienced these adverse reactions [see Warnings and Precautions (5.2, 5.3, 5.4)].

Discontinue CIPRA immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including CIPRA, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

5.2 Tendinitis and Tendon Rupture

Fluoroquinolones, including CIPRA, have been associated with an increased risk of tendinitis and tendon rupture in all ages [see Warnings and Precautions and Adverse Reactions]. 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 CIPRA, 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 CIPRA immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Avoid fluoroquinolones, including CIPRA, in patients who have a history of tendon disorders or have experienced tendinitis or tendon rupture [see Adverse Reactions].

5.3 Peripheral Neuropathy

Fluoroquinolones, including CIPRA, 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 CIPRA. Symptoms may occur soon after initiation of CIPRA and may be irreversible in some patients [see Warnings and Precautions (5.1) and Adverse Reactions.

Discontinue CIPRA 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 CIPRA, in patients who have previously experienced peripheral neuropathy [see Adverse Reactions.

5.4 Central Nervous System Effects

Fluoroquinolones, including CIPRA, have been associated with an increased risk of central nervous system (CNS) effects, including. convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis CIPRA may also cause central nervous system (CNS) events including: nervousness, agitation, insomnia, anxiety, nightmares, paranoia, dizziness, confusion, tremors, hallucinations, depression, and psychotic reactions have progressed to suicidal ideations/thoughts and self-injurious behavior such as attempted or completed suicide. These reactions may occur following the first dose. Advise patients receiving CIPRA to inform their healthcare provider immediately if these reactions occur, discontinue the drug, and institute appropriate care. CIPRA, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. As with all fluoroquinolones, use CIPRA 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). Use CIPRA when the benefits of treatment exceed the risks, since these patients are endangered because of possible undesirable CNS side effects. Cases of status epilepticus have been reported. If seizures occur, discontinue CIPRA [see Adverse Reactions (6.1) and Drug Interactions.

5.5 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including CIPRA, 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 CIPRA in patients with known history of myasthenia gravis [see Adverse Reactions.

5.6 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 CIPRA. 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 CIPRA immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted [see Adverse Reactions.

5.7 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving fluoroquinolone therapy, including CIPRA. 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 [see Adverse Reactions.

5.8 Hepatotoxicity

Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with CIPRA. 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 CIPRA [see Adverse Reactions.

5.9 Serious Adverse Reactions with Concomitant Theophylline
Serious and fatal reactions have been reported in patients receiving concurrent administration of CIPRA 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 CIPRA cannot be eliminated. If concomitant use cannot be avoided, monitor serum levels of theophylline and adjust dosage as appropriate [see Drug Interactions.

5.10 Clostridium difficile-Associated Diarrhea
Clostridium difficile (C. difficile)-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CIPRA, and may range in severity from mild diarrhea to fatal colitis.

Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing isolates of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and institute surgical evaluation as clinically indicated [see Adverse Reactions.

5.11 Prolongation of the QT Interval
Some fluoroquinolones, including CIPRA, 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 CIPRA.

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

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

In pre-clinical studies, oral administration of CIPRA caused lameness in immature dogs. Histopathological examination of the weight-bearing joints of these dogs revealed permanent lesions of the cartilage. Related quinolone-class drugs also produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species [see Use in Specific Populations
(8.4) and Nonclinical Toxicology.

5.13 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 CIPRA after sun or UV light exposure. Therefore, avoid excessive exposure to these sources of light. Discontinue CIPRA if phototoxicity occurs [see Adverse Reactions.

5.14 Development of Drug Resistant Bacteria
Prescribing CIPRA Tablets and CIPRA Oral Suspension in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

5.15 Potential Risks with Concomitant Use of Drugs Metabolized by Cytochrome P450 1A2 Enzymes
CIPRA is an inhibitor of the hepatic CYP1A2 enzyme pathway. Co-administration of CIPRA and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine) results in increased plasma concentrations of the co-administered drug and could lead to clinically significant pharmacodynamic adverse reactions of the co-administered drug [see Drug Interactions (7) and Clinical Pharmacology.

5.16 Interference with Timely Diagnosis of Syphilis
CIPRA 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 CIPRA treatment.

5.17 Crystalluria
Crystals of CIPRAfloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline [see Nonclinical Toxicology (13.2)]. Crystalluria related to CIPRAhas been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving CIPRA. Hydrate patients well to prevent the formation of highly concentrated urine [see Dosage and Administration.

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

- Disabling and Potentially Irreversible Serious Adverse Reactions [see Warnings and Precautions
- Tendinitis and Tendon Rupture [see Warnings and Precautions
- Peripheral Neuropathy [see Warnings and Precautions
- Central Nervous System Effects [see Warnings and Precautions Exacerbation of Myasthenia Gravis [see Warnings and Precautions
- Other Serious and Sometimes Fatal Adverse Reactions [see Warnings and Precautions
- Hypersensitivity Reactions [see Warnings and Precautions
- Hepatotoxicity [see Warnings and Precautions
- Serious Adverse Reactions with Concomitant Theophylline [see Warnings and Precautions
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions
- Prolongation of the QT Interval [see Warnings and Precautions
- Musculoskeletal Disorders in Pediatric Patients [see Warnings and Precautions
- Photosensitivity/Phototoxicity [see Warnings and Precautions
- Development of Drug Resistant Bacteria [see Warnings and Precautions

7 DRUG INTERACTIONS
CIPRAfloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration of CIPRA 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 9: Drugs That are Affected by and Affecting CIPRA

Drugs That are Affected by CIPRA		
Drug(s)	**Recommendation**	**Comments**
Tizanidine	Contraindicated	Concomitant administration of tizanidine and CIPRA is contraindicated due to the potentiation of hypotensive and sedative effects of tizanidine [see Contraindications
Theophylline	Avoid Use (Plasma Exposure Likely to be Increased and Prolonged)	Concurrent administration of CIPRA 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 [see Warnings and Precautions.
Drugs Known to	Avoid Use	CIPRA 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, antipsychotics) [see Warnings and Precautions (5.11) and Use in Specific Populations.
Oral antidiabetic drugs	Use with caution Glucose-lowering effect potentiated	Hypoglycemia sometimes severe has been Reported when CIPRA 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 CIPRA is co-administered with oral antidiabetic drugs [see Adverse Reactions.
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 CIPRA discontinuation in patients receiving both agents, monitor phenytoin therapy, including phenytoin serum concentration during and shortly after co-administration of CIPRA with phenytoin.
Cyclosporine	Use with caution (transient elevations in serum creatinine)	Monitor renal function (in particular serum creatinine) when CIPRA 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 CIPRA 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 CIPRA with an oral anti-coagulant (for example, warfarin).
Methotrexate	Use with caution Inhibition of methotrexate renal tubular transport potentially leading to increased methotrexate levels	Potential increase in the risk of methotrexate associated toxic reactions. Therefore, carefully monitor patients under methotrexate therapy when concomitant CIPRA 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 CIPRA [see Warnings and Precautions (5.16)].
Clozapine	Use with caution	Careful monitoring of clozapine associated Adverse reactions and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIPRA 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 [see Clinical Pharmacology.
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	CIPRA inhibits the formation of paraxanthine After caffeine administration (or pentoxifylline containing products). Monitor for xanthine toxicity and adjust dose as necessary.
Drug(s) Affecting Pharmacokinetics of CIPRA		
Antacids, Sucralfate, Multivitamins and Other Products Containing Multivalent Cations (magnesium/aluminum antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate); sucralfate; Videx® (didanosine) chewable/buffered tablets or pediatric powder; other highly buffered drugs; or products containing calcium, iron, or zinc and dairy products)	CIPRA should be taken two hours before or six hours after Multivalent cation- containing products administration and Administration (2.4)].	Decrease CIPRA absorption, resulting in lower serum and urine levels
Probenecid	Use with caution (interferes with renal tubular secretion of CIPRA and increases CIPRA serum levels)	Potentiation of CIPRA toxicity may occur.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. CIPRA 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 CIPRAfloxacin 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.2

A controlled prospective observational study followed 200 women exposed to fluoroquinolones (52.5% exposed to CIPRAfloxacin and 68% first trimester exposures) during gestation.3 In utero exposure to fluoroquinolones during embryogenesis was not associated with increased risk of major malformations. The reported rates of major congenital malformations were 2.2% for the fluoroquinolone group and 2.6%

for the control group (background incidence of major malformations is 1–5%). Rates of spontaneous abortions, 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 CIPRAfloxacin exposed children.

Another prospective follow-up study reported on 549 pregnancies with fluoroquinolone exposure (93% first trimester exposures).4 There were 70 CIPRAfloxacin exposures, all within the first trimester. The malformation rates among live-born babies exposed to CIPRAfloxacin 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 CIPRAfloxacin.

No differences in the rates of prematurity, spontaneous abortions, or birth weight were seen in women exposed to CIPRAfloxacin during pregnancy.2, 3 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 CIPRAfloxacin in pregnant women and their developing fetuses.

Reproduction studies have been performed in rats and mice using oral doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and have revealed no evidence of harm to the fetus due to CIPRAfloxacin. In rabbits, oral CIPRAfloxacin dose levels of 30 and 100 mg/kg (approximately 0.4-and 1.3-times the highest recommended therapeutic dose based upon body surface area) produced gastrointestinal toxicity resulting in maternal weight loss and an increased incidence of abortion, but no teratogenicity was observed at either dose level. After intravenous administration of doses up to 20 mg/kg (approximately 0.3-times the highest recommended therapeutic dose based upon body surface area), no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed.

8.2 Nursing Mothers

CIPRAfloxacin is excreted in human milk. The amount of CIPRAfloxacin 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 CIPRA, 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.

8.3 Pediatric Use

Although effective in clinical trials, CIPRA is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls. Quinolones, including CIPRA, cause arthropathy in juvenile animals [see Warnings and Precautions and Nonclinical Toxicology.

Complicated Urinary Tract Infection and Pyelonephritis

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

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

8.4 Geriatric Use
Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as CIPRA. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing CIPRA to elderly patients especially those on corticosteroids. Patients should be informed of this potential adverse reaction and advised to discontinue CIPRA and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur. [see Boxed Warning, Warnings and Precautions (5.2), and Adverse Reactions.

In a retrospective analysis of 23 multiple-dose controlled clinical trials of CIPRA encompassing over 3500 CIPRAfloxacin-treated patients, 25% of patients were greater than or equal to 65 years of age and 10% were greater than or equal to 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals on any drug therapy cannot be ruled out. CIPRAfloxacin is known to be substantially excreted by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. No alteration of dosage is necessary for patients greater than 65 years of age with normal renal function. However, since some older individuals experience reduced renal function by virtue of their advanced age, care should be taken in dose selection for elderly patients, and renal function monitoring may be useful in these patients [see Dosage and Administration (2.3) and Clinical Pharmacology.

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

8.5 Renal Impairment
CIPRAfloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction [see Dosage and Administration (2.3) and Clinical Pharmacology.

8.6 Hepatic Impairment
In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in CIPRAfloxacin pharmacokinetics have been observed. The pharmacokinetics of CIPRAfloxacin in patients with acute hepatic insufficiency, have not been studied.

9 OVERDOSAGE
In the event of acute overdosage, reversible renal toxicity has been reported in some cases. Empty the stomach by inducing vomiting or by gastric lavage. Observe the patient carefully and give supportive treatment, including monitoring of renal function, urinary pH and acidify, if required, to prevent crystalluria and administration of magnesium, aluminum, or calcium containing antacids which can reduce the absorption of CIPRAfloxacin. Adequate hydration must be maintained. Only a small amount of CIPRAfloxacin (less than 10%) is removed from the body after hemodialysis or peritoneal dialysis.

9.1 Microbiology
Mechanism of Action
The bactericidal action of CIPRAfloxacin 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 CIPRAfloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to CIPRAfloxacin. Resistance to fluoroquinolones occurs primarily by either mutations in the DNA gyrases, decreased outer membrane permeability, or drug efflux. In vitro resistance to CIPRAfloxacin develops slowly by multiple step mutations. Resistance to CIPRAfloxacin 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 CIPRAfloxacin and other classes of antimicrobials.

CIPRAfloxacin has been shown to be active against most isolates of the following bacteria, both in vitro and in clinical infections [see Indications and Usage.

Gram-positive bacteria
Bacillus anthracis
Enterococcus faecalis
Staphylococcus aureus (methicillin-susceptible isolates only)
Staphylococcus epidermidis (methicillin-susceptible isolates only)
Staphylococcus saprophyticus
Streptococcus pneumoniae
Streptococcus pyogenes

Gram-negative bacteria
Campylobacter jejuni
Citrobacter koseri
Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas aeruginosa
Salmonella typhi
Serratia marcescens
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Yersinia pestis

The following in vitro data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an in vitro minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for CIPRAfloxacin (≤1 mcg/mL). However, the efficacy of CIPRAfloxacin 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 aerogenes
Klebsiella oxytoca
Legionella pneumophila
Pasteurella multocida
Salmonella enteritidis

Vibrio cholerae
Vibrio parahaemolyticus
Vibrio vulnificus
Yersinia enterocolitica
Susceptibility Test Methods

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

10. HOW SUPPLIED

Cipra 250 mg film coated tablets: Alu. Alu. Blister pack of 10 tablets.
Cipra 500 mg film coated tablets: Alu. Alu. Blister pack of 10 tablets.

STORAGE AND HANDLING

Store below 25°C (77°F); excursions are permitted from 15°C to 30°C (59°F to 86°F).
Protect from sunlight and moisture
Keep out of reach of children.

سپرا ٹیبلیٹ

(سپروفلاکساسن)

۲۵۰ ملی گرام اور ۵۰۰ ملی گرام ٹیبلیٹ

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: صرف مستعد ڈاکٹر کے نسخے پر فروخت کی جائے۔

۲۵° ڈگری سے کم درجہ حرارت پر رکھیں۔

دھوپ اور نمی سے بچائیں۔ بچوں کی پہنچ سے دور رکھیں۔

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NAWAN LABORATORIES (PVT) LTD.
136, Sector 15, Korangi Industrial Area, Karachi-74900, Pakistan.