Cyrocin®

(Ciprofloxacin)

Highnoon

COMPOSITION

Cyrocin 125mg/5mL dry powder suspension:
Each 5mL contains: Ciprofloxacin (as hydrochloride) 125mcg

Cyrocin 250mg/5mL dry powder suspension:
Each 5mL contains: Ciprofloxacin (as hydrochloride) 250mcg

DESCRIPTION

Cyrocin (ciprofloxacin hydrochloride) is fluorinated 4 – quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid and more favourable pharmacokinetics allowing its use in systemic infections.

MECHANISM OF ACTION

Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents. Ciprofloxacin is a broad-spectrum antibiotic that is active against both Gram- positive and Gram-negative bacteria. 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.

PHARMACOKINETICS

Ciprofloxacin is readily and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70% to 80% and a peak plasma concentration of about 2.4 micrograms/mL, occurs 1 to 2 hours after a 500mg oral dose. Absorption of the ciprofloxacin may be delayed by the presence of food, but is not substantially affected overall.
The binding of ciprofloxacin to serum proteins is 20% to 40% which is not likely to be high enough 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 genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humour of the eye. 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.
The elimination half-life is about 3 hours to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. There is limited information on effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of liver.
Ciprofloxacin is eliminated principally by urinary excretion, but non renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified, oxociprofloxacin appears to be the major urinary metabolites. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid: it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as of metabolites. Up to 70% of parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days have accounted for 20 to 35% of an oral dose and 15% of an intravenous dose. Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

MICROBIOLOGY

Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both in vitro 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 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.

INDICATIONS AND USAGE

It is indicated for treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions and patient populations listed below.

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

Chronic Bacterial Prostatitis
It is indicated in adult patients for treatment of chronic bacterial prostatitis caused by Escherichia coli or Proteus mirabilis.

Lower Respiratory Tract Infections
It 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. It is also indicated for the treatment of acute exacerbations of chronic bronchitis caused by Moraxella catarrhalis.

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

Skin and Skin Structure Infections
It 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
It is indicated in adult patients for treatment of bone and joint infections caused by Enterobacter cloacae, Serratia marcescens, or Pseudomonas aeruginosa.

Complicated Intra-Abdominal Infections
It 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 Diarrhoea
It is indicated in adult patients for treatment of infectious diarrhoea caused by Escherichia coli (enterotoxigenic isolates), Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri or Shigella sonnei when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever)
It 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 Gonorrhoea
It is indicated in adult patients for treatment of uncomplicated cervical and urethral gonorrhoea due to Neisseria gonorrhoeae.

Complicated Urinary Tract Infections and Pyelonephritis
It is indicated in paediatric patients 1 year to 17 years of age for treatment of complicated urinary tract infections (cUTI) and pyelonephritis due to Escherichia coli.

Inhalational Anthrax (Post-exposure)
It is indicated in adults and paediatric 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.

Plague
It is indicated for treatment of plague, including pneumonic and septicaemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and paediatric patients from birth to 17 years of age. Ciprofloxacin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. 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.
Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to Streptococcus pneumoniae.

DOSAGE AND ADMINISTRATION

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

Dosage in Paediatric Patients
Dosing and initial route of oral therapy for complicated UTI or pyelonephritis should be determined by the severity of the infection. Ciprofloxacin should be administered as described:

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 days to 21 days
Inhalational Anthrax (Post Exposure)	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	60 days
Plague	15 mg/kg (maximum 500 mg per dose)	Every 8 to 12 hours	14 days

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 for use in patients with renal impairment are:

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 haemodialysis or Peritoneal dialysis	250-500 mg every 24 hours (after dialysis)

CONTRAINDICATIONS

- It is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterial, or any of the product components.
- Concomitant administration with tizanidine is contraindicated.

ADVERSE EFFECTS

The reported adverse events of ciprofloxacin are: tendinopathy and tendon rupture, exacerbation of Myasthenia Gravis, hepatotoxicity, QT prolongation, hypersensitivity reactions including serious and fatal reactions, serious adverse reactions with concomitant theophylline, clostridium difficile-associated diarrhoea, peripheral neuropathy, musculoskeletal disorders in paediatric patients, photosensitivity/ phototoxicity, development of drug resistant bacteria, gastrointestinal disturbances include nausea, diarrhoea, vomiting, constipation, abdominal pain, dyspepsia, pseudomembranous colitis, pancreatitis, abdominal distention, gastrointestinal bleeding, intestinal perforation, dysphagia, headache, dizziness, confusion, insomnia, tremors, drowsiness, restlessness, nightmares, lethargy, abnormal gait, agitation, anxiety, hallucination, psychotic reactions, depressions, convulsions, intracranial hypertension, paraesthesia, paranoia, irritability, ataxia, anorexia, phobia, migraine, hypertonia, twitching, polyneuropathy, rash, pruritus, skin reactions included vasculitis, erythema multiforme, Stevens-Johsons syndrome, urticaria, fever, exfoliative dermatitis, flushing, angioedema, erythema nodosum, exfoliative dermatitis, fixed eruption, serum sickness like reactions, acute generalized exanthematous pustulosis, petechia, toxic epidermal necrolysis, reversible arthralgia, joint stiffness, myoclonus, myalgia, muscle weakness in patient with myasthenia gravis, severe exacerbation leading to respiratory failure or death, elevated liver enzyme values jaundice, hepatitis, tachycardia, hypotension, oedema, syncope, hot flushes, sweating, angina pectoris, myocardial infarction, cardiopulmonary arrest, Torssade de Points and ventricular arrhythmia. Special senses adverse effects include blurred vision, disturbed vision, decreased visual acuity, diplopia, tinnitus, hearing loss, bad taste, anosmia, hyperesthesia and taste loss. Renal effects include acute renal failure, dysuria, interstitial nephritis, acute tubular necrosis, transient increase in serum creatinine, or blood urea nitrogen, crystalluria, dyspnoea, laryngeal oedema, haemoptysis, bronchospasm, hypoglycaemia, hyperglycaemia, haematological disturbances including eosinophilia, thrombocytopenia, leukopenia and very rarely pancytopenia, haemolytic anaemia, agranulocytosis, neutropenia, prothrombin time prolongation or decrease, cholesterol elevation and potassium elevation.

DRUG INTERACTIONS

- Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as clozapine, ropinirole, theophylline and tizanidine, that are metabolized by this isoenzyme. Use of fluoroquinolones with tizanidine is contraindicated (due to potentiation of hypotensive and sedative effects of tizanidine), although theophylline may be used providing its dose is reduced and concentrations monitored. Clozapine or ropinirole may also be used, providing appropriate clinical surveillance occurs with subsequent dose adjustment where necessary.
- The ciprofloxacin should be taken at least two hours before or six hours after multivitamin cation-containing products administration. Antacids, sucralfate, multivitamins and other products containing multivalent cations (magnesium / aluminium antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate); sucralfate; didanosine chewable/buffered tablets or paediatric powder; other highly buffered drugs; or products containing calcium, iron, or zinc and dairy products) decrease ciprofloxacin absorption, resulting in lower serum and urine levels.
- Quinolones, including ciprofloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are ris k factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.
- Disturbances of blood glucose, including hypoglycaemia have been reported in patients treated concomitantly with ciprofloxacin and an antidiabetic agents mainly sulfonylurea (for example glyburide, glimepiride). Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered. If a hypoglycaemic reaction occurs, ciprofloxacin should be discontinued and appropriate therapy should be initiated immediately.
- Altered serum levels of phenytoin (increased and decreased) – to avoid the loss of seizure control associated with decreased phenytoin levels and to prevent phenytoin overdose-related adverse reactions upon ciprofloxacin discontinuation in patients receiving both agents, monitor phenytoin therapy, including phenytoin serum concentration during and shortly after co administration of ciprofloxacin with phenytoin.
- coadministration administration of a nonsteroidal anti-inflammatory drugs (but not acetyle salicyclic acid) with a quinolone may increase the risks of CNS stimulation and convulsions. Fluoroquinolones also interact with opioid analgesic.
- Some fluoroquinolones have the potential to prolong the QT interval and should be avoided in patients also receiving class I a antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmic, drugs (such as amiodarone & sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).
- The excretion of fluoroquinolones is reduced and plasma concentrations may be increased by probenecid. Potentiation of ciprofloxacin toxicity may occur.
- Transient increase in serum creatinine has occurred when fluoroquinolones is given with cyclosporin; monitoring of serum creatinine concentrations is recommended.
- Inhibition of methotrexate renal tubular transport potentially leading to increased methotrexate plasma levels. Therefore, carefully monitor patients under methotrexate therapy when concomitant ciprofloxacin therapy is indicated.
- Caution should be exercised when used with sildenafil (two-fold increase in exposure). Carefully monitor for sildenafil toxicity.
- Avoid use with duloxetine (five-fold increase in duloxetine exposure) – if unavoidable, monitor for duloxetine toxicity. Ciprofloxacin inhibits the formation of paraxanthine after caffeine administration (or pentoxifylline containing products). Carefully, monitor for xanthine toxicity and adjust dose as necessary.

WARNINGS AND PRECAUTIONS

The following precaution and warning should be measured during ciprofloxacin treatment:

- Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. The reported events includes the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. The most frequently involves the Achilles tendon, rupture of the Achilles tendon. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Inflammation and tendon rupture can occur, sometimes bilaterally, even within the first 48 hours, during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin should be used with caution in patients with a history of tendon disorders. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.
- Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including ciprofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Ciprofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. 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.
- Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain aetiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:
  - Fever, rash, or severe dermatologic reactions (e.g., 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;
  - Anaemia, including haemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted.

- Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with ciprofloxacin. 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 and fatal reactions have been reported in patients receiving concurrent administration of 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.
- Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events. 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. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. 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). Use ciprofloxacin 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 ciprofloxacin.
- Clostridium difficile (C, difficile) - associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea 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.
- 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. 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.
- Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and cases of arrhythmia. 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 hypokalaemia 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.
- Quinolone antibiotics may make your skin become more sensitive to sunlight or UV light. You should avoid prolonged exposure to sunlight or strong sunlight and should not use a sunbed or any other UV lamp while taking ciprofloxacin. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.
- Prescribing ciprofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving ciprofloxacin. Hydrate patients well to prevent the formation of highly concentrated urine.
- 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 gonorrhoea may mask or delay the symptoms of incubating syphilis. Perform a serologic test for syphilis in all patients with gonorrhoea at the time of diagnosis. Perform follow-up serologic test for syphilis three months after ciprofloxacin treatment.
- 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.

USE IN SPECIFIC POPULATIONS

Pregnancy
Pregnancy Category C. Because no adequate or well-controlled studies have been conducted in pregnant women, ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers
Ciprofloxacin is excreted in the breast milk. 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.

Paediatric Use
Ciprofloxacin is not a drug of first choice in the paediatric population due to an increased incidence of adverse reactions compared to the controls, including events related to joints and/or surrounding tissues.

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

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.

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

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, aluminium, or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (less than 10%) is removed from the body after haemodialysis or peritoneal dialysis.

DIRECTION FOR PREPARING SUSPENSION:

Tap the bottle to loosen the powder, open the cap of the bottle and add 5 spoons (25mL) of boiled cooled water, replace the cap and shake well. Further add water up to the mark on the label and shake vigorously until uniform suspension is prepared.
Reconstituted suspension should be used within 7 days if stored at room temperature or within 14 days of refrigerated. After reconstitution keep tightly closed. Avoid freezing. Shake well before taking each dose.

DOSAGE AND INSTRUCTIONS

To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30°C. Keep in dry place. Protect from light.

PRESENTATION

Cyrocin 125mg/5mL dry powder suspension:
Glass amber bottle of 60mL
Cyrocin 250mg/5mL dry powder suspension:
Glass amber bottle of 60mL

سائروسین®

(سپروفلوکساسین)

سسپنشن تیار کرنے کا طریقہ:

بوتل کو اچھی طرح ہلائیں تاکہ اس میں موجود پاؤڈر بوتل کی دیواروں سے علیحدہ ہو جائے۔ دوا تیار کرنے کیلئے پہلے ۵ چمچ (۲۵ ملی لیٹر) اُبلا ہوا ٹھنڈا پانی ڈالیں اور بوتل کو اچھی طرح ہلا لیں۔ پھر مزید اتنا پانی ڈالیں کہ بوتل پر دیئے ہوئے نشان تک سسپنشن تیار ہو جائے۔ سسپنشن کو اچھی طرح ہلا لیں۔ تیار کیا ہوا سسپنشن ۷ دن کے اندر کمرے کے درجہ حرارت پر اور ریفریجریٹر میں ۱۴ دن کے اندر استعمال کریں۔

سسپنشن بنانے کے بعد ڈھکن کو اچھی طرح بند رکھیں۔

دوا کو منجمد ہونے سے بچائیں۔

استعمال سے پہلے دوا کو اچھی طرح ہلا لیں۔

خوراک و ہدایات:

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت اور استعمال کی جائے۔
بچوں کی پہنچ سے دور رکھیں۔ 30°C سے زیادہ درجہ حرارت پر نہ رکھیں۔
خشک جگہ پر رکھیں۔ روشنی سے بچائیں۔

Manufactured by
HIGHNOON LABORATORIES LTD
17.5 KM, Multan Road, Lahore, Pakistan.
www.highnoon-labs.com

Item Code No. 14002745

Cyrocin®

(Ciprofloxacin)

Highnoon

COMPOSITION
Cyrocin 250mg Tablet: Each film-coated tablet contains: Ciprofloxacin (as hydrochloride) 250mg

Cyrocin 500mg Tablet: Each film-coated tablet contains: Ciprofloxacin (as hydrochloride) 500mg

DESCRIPTION
Cyrocin (ciprofloxacin hydrochloride) is fluorinated 4 – quinolone or fluoroquinolone antibacterial with a wider spectrum of activity than nalidixic acid and more favourable pharmacokinetics allowing its use in systemic infections.

MECHANISM OF ACTION
Ciprofloxacin is a member of the fluoroquinolone class of antibacterial agents. Ciprofloxacin is a broad-spectrum antibiotic that is active against both Gram- positive and Gram-negative bacteria. 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.

PHARMACOKINETICS
Ciprofloxacin is readily and well absorbed from the gastrointestinal tract. Oral bioavailability is about 70% to 80% and a peak plasma concentration of about 2.4 micrograms/mL, occurs 1 to 2 hours after a 500 mg oral dose. Absorption of the ciprofloxacin may be delayed by the presence of food, but is not substantially affected overall.
The binding of ciprofloxacin to serum proteins is 20% to 40% which is not likely to be high enough 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 genital tissue including the prostate. Ciprofloxacin is present in active form in the saliva, nasal and bronchial secretions, mucosa of the sinuses, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. Ciprofloxacin has also been detected in lung, skin, fat, muscle, cartilage, and bone. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humour of the eye. 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.
The elimination half-life is about 3 hours to 5 hours and there is evidence of modest accumulation. Half-life may be prolonged in renal impairment (a value of 8 hours has been reported in end-stage renal disease) and to some extent in the elderly. There is limited information on effect of hepatic impairment; the half-life of ciprofloxacin has been reported to be slightly prolonged in patients with severe cirrhosis of liver.
Ciprofloxacin is eliminated principally by urinary excretion, but non renal clearance may account for about one-third of elimination and includes hepatic metabolism, biliary excretion, and possibly transluminal secretion across the intestinal mucosa. At least 4 active metabolites have been identified, oxociprofloxacin appears to be the major urinary metabolites. Urinary excretion is by active tubular secretion as well as glomerular filtration and is reduced by probenecid: it is virtually complete within 24 hours. About 40 to 50% of an oral dose is excreted unchanged in the urine and about 15% as of metabolites. Up to 70% of parenteral dose may be excreted unchanged within 24 hours and 10% as metabolites. Faecal excretion over 5 days have accounted for 20 to 35% of an oral dose and 15% of an intravenous dose. Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

MICROBIOLOGY
Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both in vitro 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 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.

INDICATIONS AND USAGE
It is indicated for treatment of infections caused by susceptible isolates of the designated microorganisms in the conditions and patient populations listed below.

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

Chronic Bacterial Prostatitis
It is indicated in adult patients for treatment of chronic bacterial prostatitis caused by Escherichia coli or Proteus mirabilis.

Lower Respiratory Tract Infections
It 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. It is also indicated for the treatment of acute exacerbations of chronic bronchitis caused by Moraxella catarrhalis.

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

Skin and Skin Structure Infections
It 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
It is indicated in adult patients for treatment of bone and joint infections caused by Enterobacter cloacae, Serratia marcescens, or Pseudomonas aeruginosa.

Complicated Intra-abdominal Infections
It 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 Diarrhoea
It is indicated in adult patients for treatment of infectious diarrhoea caused by Escherichia coli (enterotoxigenic isolates), Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri or Shigella sonnei when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever)
It 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 Gonorrhoea
It is indicated in adult patients for treatment of uncomplicated cervical and urethral gonorrhoea due to Neisseria gonorrhoeae.

Complicated Urinary Tract Infections and Pyelonephritis
It is indicated in paediatric patients 1 year to 17 years of age for treatment of complicated urinary tract infections (cUTI) and pyelonephritis due to Escherichia coli.

Inhalational Anthrax (Post-exposure)
It is indicated in adults and paediatric 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.

Plague
It is indicated for treatment of plague, including pneumonic and septicaemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and paediatric patients from birth to 17 years of age. Ciprofloxacin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. 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.
Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to Streptococcus pneumoniae.

DOSAGE AND ADMINISTRATION
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-defence mechanisms, and the status of renal and hepatic function. If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Adult Dosage

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

1. Used in conjunction with metronidazole.
2. Begin drug administration as soon as possible after suspected or confirmed exposure.

Dosage in Paediatric Patients
Dosing and initial route of oral therapy for complicated UTI or pyelonephritis should be determined by the severity of the infection. Ciprofloxacin should be administered as described:

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 days to 21 days
Inhalational Anthrax (Post Exposure)	15 mg/kg (maximum 500 mg per dose)	Every 12 hours	60 days
Plague	15 mg/kg (maximum 500 mg per dose)	Every 8 to 12 hours	14 days

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 for use in patients with renal impairment are:
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 haemodialysis or Peritoneal dialysis	250-500 mg every 24 hours (after dialysis)

CONTRAINDICATIONS
- It is contraindicated in persons with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antibacterial, or any of the product components.
- Concomitant administration with tizanidine is contraindicated.

ADVERSE EFFECTS
The reported adverse events of ciprofloxacin are: tendinopathy and tendon rupture, exacerbation of Myasthenia Gravis, hepatotoxicity, QT prolongation, hypersensitivity reactions including serious and fatal reactions, serious adverse reactions with concomitant theophylline, clostridium difficile-associated diarrhoea, peripheral neuropathy, musculoskeletal disorders in paediatric patients, photosensitivity/ phototoxicity, development of drug resistant bacteria, gastrointestinal disturbances include nausea, diarrhoea, vomiting, constipation, abdominal pain, dyspepsia, pseudomembranous colitis, pancreatitis, abdominal distention, gastrointestinal bleeding, intestinal perforation, dysphagia, headache, dizziness, confusion, insomnia, tremors, drowsiness, restlessness, nightmares, lethargy, abnormal gait, agitation, anxiety, hallucination, psychotic reactions, depressions, convulsions, intracranial hypertension, paraesthesia, paranoia, irritability, ataxia, anorexia, phobia, migraine, hypertonia, twitching, polyneuropathy, rash, pruritus, skin reactions included vasculitis, erythema multiforme, Stevens-Johsons syndrome, urticaria, fever, exfoliative dermatitis, flushing, angioedema, erythema nodosum, exfoliative dermatitis, fixed eruption, serum sickness like reactions, acute generalized exanthematous pustulosis, petechia, toxic epidermal necrolysis, reversible arthralgia, joint stiffness, myoclonus, myalgia, muscle weakness in patient with myasthenia gravis, severe exacerbation leading to respiratory failure or death, elevated liver enzyme values jaundice, hepatitis, tachycardia, hypotension, oedema, syncope, hot flushes, sweating, angina pectoris, myocardial infarction, cardiopulmonary arrest, Torssade de Points and ventricular arrhythmia. Special senses adverse effects include blurred vision, disturbed vision, decreased visual acuity, diplopia, tinnitus, hearing loss, bad taste, anosmia, hyperesthesia and taste loss. Renal effects include acute renal failure, dysuria, interstitial nephritis, acute tubular necrosis, transient increase in serum creatinine, or blood urea nitrogen, crystalluria, dyspnoea, laryngeal oedema, haemoptysis, bronchospasm, hypoglycaemia, hyperglycaemia, haematological disturbances including eosinophilia, thrombocytopenia, leukopenia and very rarely pancytopenia, haemolytic anaemia, agranulocytosis, neutropenia, prothrombin time prolongation or decrease, cholesterol elevation and potassium elevation.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category C. Because no adequate or well-controlled studies have been conducted in pregnant women, ciprofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Nursing Mothers
Ciprofloxacin is excreted in the breast milk. 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.

Paediatric Use
Ciprofloxacin is not a drug of first choice in the paediatric population due to an increased incidence of adverse reactions compared to the controls, including events related to joints and/or surrounding tissues.

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

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.

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

DRUG INTERACTIONS
- Fluoroquinolones, including ciprofloxacin, are known to inhibit the cytochrome P450 isoenzyme CYP1A2 and may increase plasma concentrations of drugs, such as clozapine, ropinirole, theophylline and tizanidine, that are metabolized by this isoenzyme. Use of fluoroquinolones with tizanidine is contraindicated (due to potentiation of hypotensive and sedative effects of tizanidine), although theophylline may be used providing its dose is reduced and concentrations monitored. Clozapine or ropinirole may also be used, providing appropriate clinical surveillance occurs with subsequent dose adjustment where necessary.
- The ciprofloxacin should be taken at least two hours before or six hours after multivitamin cation-containing products administration. Antacids, sucralfate, multivitamins and other products containing multivalent cations (magnesium / aluminium antacids; polymeric phosphate binders (for example, sevelamer, lanthanum carbonate); sucralfate; didanosine chewable/buffered tablets or paediatric powder; other highly buffered drugs; or products containing calcium, iron, or zinc and dairy products) decrease ciprofloxacin absorption, resulting in lower serum and urine levels.
- Quinolones, including ciprofloxacin, have been reported to enhance the anticoagulant effects of warfarin or its derivatives in the patient population. In addition, infectious disease and its accompanying inflammatory process, age, and general status of the patient are risk factors for increased anticoagulant activity. Therefore the prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if a quinolone is administered concomitantly with warfarin or its derivatives.
- Disturbances of blood glucose, including hypoglycaemia have been reported in patients treated concomitantly with ciprofloxacin and an antidiabetic agents mainly sulfonylurea (for example glyburide, glimepiride). Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered. If a hypoglycaemic reaction occurs, ciprofloxacin should be discontinued and appropriate therapy should be initiated immediately.
- 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 coadministration of ciprofloxacin with phenytoin.
- Concomitant administration of a nonsteroidal anti-inflammatory drugs (but not acetyle salicyclic acid) with a quinolone may increase the risks of CNS stimulation and convulsions. Fluoroquinolones also interact with opioid analgesic.
- Some fluoroquinolones have the potential to prolong the QT interval and should be avoided in patients also receiving class I a antiarrhythmic drugs (such as quinidine and procainamide) or class III antiarrhythmic, drugs (such as amiodarone & sotalol). In addition, caution should be exercised when they are used with other drugs known to have this effect (such as the antihistamines astemizole and terfenadine, cisapride, erythromycin, pentamidine, phenothiazines, or tricyclic antidepressants).
- The excretion of fluoroquinolones is reduced and plasma concentrations may be increased by probenecid. Potentiation of ciprofloxacin toxicity may occur.
- Transient increase in serum creatinine has occurred when fluoroquinolones is given with cyclosporin; monitoring of serum creatinine concentrations is recommended.
- Inhibition of methotrexate renal tubular transport potentially leading to increased methotrexate plasma levels. Therefore, carefully monitor patients under methotrexate therapy when concomitant ciprofloxacin therapy is indicated.
- Caution should be exercised when used with sildenafil (two-fold increase in exposure). Carefully monitor for sildenafil toxicity.
- Avoid use with duloxetine (five-fold increase in duloxetine exposure) – if unavoidable, monitor for duloxetine toxicity. Ciprofloxacin inhibits the formation of paraxanthine after caffeine administration (or pentoxifylline containing products). Carefully, monitor for xanthine toxicity and adjust dose as necessary.

WARNINGS AND PRECAUTIONS
The following precaution and warning should be measured during ciprofloxacin treatment:

- Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. The reported events includes the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. The most frequently involves the Achilles tendon, rupture of the Achilles tendon. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Inflammation and tendon rupture can occur, sometimes bilaterally, even within the first 48 hours, during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin should be used with caution in patients with a history of tendon disorders. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.
- Fluoroquinolones, including ciprofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy, including ciprofloxacin. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Ciprofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. 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.
- Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain aetiology, have been reported rarely in patients receiving therapy with quinolones, including ciprofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:
  - o Fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
  - o Vasculitis; arthralgia; myalgia; serum sickness;
  - o Allergic pneumonitis;
  - o Interstitial nephritis; acute renal insufficiency or failure;
  - o Hepatitis; jaundice; acute hepatic necrosis or failure;
  - o Anaemia, including haemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted

- Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure, and fatal events, have been reported with ciprofloxacin. 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 and fatal reactions have been reported in patients receiving concurrent administration of 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.
- Convulsions, increased intracranial pressure (including pseudotumor cerebri), and toxic psychosis have been reported in patients receiving fluoroquinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events. 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. Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. 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). Use ciprofloxacin 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 ciprofloxacin.
- Clostridium difficile (C. difficile) - associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea 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.
- 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. 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.
- Some fluoroquinolones, including ciprofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and cases of arrhythmia. 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 hypokalaemia 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.
- Quinolone antibiotics may make your skin become more sensitive to sunlight or UV light. You should avoid prolonged exposure to sunlight or strong sunlight and should not use a sunbed or any other UV lamp while taking ciprofloxacin. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.
- Prescribing ciprofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.
- Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Avoid alkalinity of the urine in patients receiving ciprofloxacin. Hydrate patients well to prevent the formation of highly concentrated urine.
- 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 gonorrhoea may mask or delay the symptoms of incubating syphilis. Perform a serologic test for syphilis in all patients with gonorrhoea at the time of diagnosis. Perform follow-up serologic test for syphilis three months after ciprofloxacin treatment.
- 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.

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, aluminium, or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (less than 10%) is removed from the body after haemodialysis or peritoneal dialysis.

DOSAGE AND INSTRUCTIONS
To be sold and used on the prescription of a registered medical practitioner only. Keep out of reach of children. Do not store above 30ºC. Keep in dry place. Protect from light.

PRESENTATION
Cyrocin 250mg Tablets:
Alu. PVC Blister pack of 1 x 10's.
Cyrocin 500mg Tablets:
Alu. PVC Blister pack of 1 x 10's.

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(سپروفلوکساسین)

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