Ciplet

(Ciprofloxacin)

COMPOSITION:
Ciplet Tablets 250mg
Each film coated tablet contains:
Ciprofloxacin ……..... 250mg
Finished Product Specs.: USP.
Ciplet Tablets 500mg
Each film coated tablet contains:
Ciprofloxacin ……..... 500mg
Finished Product Specs.: USP.
Ciplet Oral Suspension 125mg/5ml
Each 5ml suspension contains:
Ciprofloxacin……..... 125mg
Finished Product Specs.: USP.
Ciplet Oral Suspension 250mg/5ml
Each 5ml suspension contains:
Ciprofloxacin……..... 250mg
Finished Product Specs.: USP.
Ciplet IV Infusion 200mg/100ml
Each 100ml vial contains:
Ciprofloxacin …..... 200mg
(As Ciprofloxacin Lactate).
Finished Product Specs.: BP
Ciplet DS IV Infusion 400mg/100ml
Each 100ml vial contains:
Ciprofloxacin…..... 400mg
(As Ciprofloxacin Lactate).
Finished Product Specs.: BP

PHARMACOLOGICAL ACTION:
Pharmacodynamic:
Mechanism of action:
As a fluoroquinolones antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.
Mechanism of resistance:
In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutation in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Pharmacokinetics:
Absorption:
Following oral administration of single doses of 250 mg, 500 mg and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. The absolute bioavailability is approximately 70–80%.
Distribution:
Protein binding of ciprofloxacin is low (20-30%) Ciprofloxacin is present in plasma largely in a non -ionised form and has a large steady state distribution volume of 2–3 L/kg body weight.
Metabolism:
Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.
Elimination:
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4–7 hours.

INDICATIONS:
Adults:
1. Uncomplicated acute cystitis.
2. Acute exacerbations of chronic bronchitis and of chronic obstructive pulmonary disease.
3. Acute bacterial sinusitis.
4. Otitis media acute.

In above mentioned condition, Ciplet should be used only when it is onsidered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

5. Acute pyelonephritis.
6. Complicated urinary tract infections.
7. Bacterial prostatitis.
8. Infections of the bones and joints.
9. Gonococcal uretritis and cervicitis due to susceptible Neisseria gonorrhoeae.
10. Infections of the skin and soft tissue caused by Gram-negative bacteria.
11. Inhalation anthrax (post-exposure prophylaxis and curative treatment).
12. Typhoid fever.
13. Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Children and adolescents:
1. Broncho-pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis.
2. Complicated urinary tract infections and acute pyelonephritis.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

DOSAGE AND ADMINISTRATION:
Ciplet IV Infusion: The usual dose is 100mg - 200mg IV every 12 hours. Forsevere and/or complicated infections 400mg may be administered every 12 hours (i.e. bd). Intravenous therapy should be discontinued as soon as oral ciprofloxacin therapy can be substituted. The normal duration of intravenous therapy is up to 7 days.
In cystic fibrosis patients the normal dose is 200mg IV twice daily. The low body mass of these patients should, however, be taken into consideration when determining dosage (5-10mg/kg/day).
Ciplet IV should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with the other compatible infusion solutions. The Ciplet IV infusion solution is compatible with physiological saline, Ringer solution and Ringer lactate solution, 5% and 10% glucose solutions, 10% fructose solution, and 5% glucose solution with 0.225% NaCl or 0.45% NaCl When ciprofloxacin infusion solutions are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.

Ciplet Tablets and Oral Suspension:
Adults: Ciplet Tablets and Ciplet Oral Suspension should be administered orally to adults as described in the Dosage Guidelines table.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection.

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required.

ADULT DOSAGE GUIDELINES

Infections	Severity	Dose	Frequency	Usual Durations†
Urinary Tract	Acute Uncomplicated	250mg	q 12 hrs	3 days
	Mild/Moderate	250mg	q 12 hrs	7-14 days
	Severe/Complicated	500mg	q 12 hrs	7-14 days
Chronic Bacterial Prostatitis	Mild/Moderate	500mg	q 12 hrs	28 days
Lower Respiratory Tract	Mild/Moderate	500mg	q 12 hrs	7-14 days
	Severe/Complicated	750mg	q 12 hrs	7-14 days
Acute Sinusitis	Mild/Moderate	500mg	q 12 hrs	10 days
Skin and Skin Structure	Mild/Moderate	500mg	q 12 hrs	7-14 days
	Severe/Complicated	750mg	q 12 hrs	7-14 days
Bone and Joint	Mild/Moderate	500mg	q 12 hrs	≥ 4-6 weeks
	Severe/Complicated	750mg	q 12 hrs	≥ 4-6 weeks
Intra-Abdominal*	Complicated	500mg	q 12 hrs	7-14 days
Infectious Diarrhea	Mild/Moderate/Severe	500mg	q 12 hrs	5-7 days
Typhoid Fever	Mild/Moderate	500mg	q 12 hrs	10 days
Urethral & Cervical Gonococcal Infections	Uncomplicated	250mg	Single dose	Single dose
Inhalational anthrax (post-exposure)**	-	500mg	q 12 hrs	60 days

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

Conversion of IV to Oral Dosing in Adults
Patients whose therapy is started with Ciplet IV may be switched to Ciplet Tablets or Ciplet Oral Suspension when clinically indicated at the discretion of the physician.

Equivalent AUC Dosing Regimens

Ciplet Oral Dosage	Equivalent Ciplet I.V. Dosage
250mg Tablet q 12 hrs	200mg I.V. q 12 hrs
500mg Tablet q 12 hrs	400mg I.V. q 12 hrs
750mg Tablet q 12 hrs	400mg I.V. q 8 hrs

Adults with Impaired Renal Function
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. The following table provides dosage guidelines for use in patients with renal impairment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (ml/min)	Dose
> 50	See Usual Dosage
30 - 50	250 - 500mg q 12 hrs
5 - 29	250 - 500mg q 18 hrs
Patients on hemodialysis or Peritoneal dialysis	250 - 500mg q 24 hrs (after dialysis)

When only the serum creatinine concentration is known, the following formula 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 750mg may be administered at the intervals noted above. Patients should be carefully monitored.
Pediatrics
Ciplet Tablets and Ciplet Oral Suspension should be administered orally as

described in the Dosage Guidelines table. An increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues, has been observed.

Dosing and initial route of therapy (i.e., IV or oral) for complicated urinary tract infection or pyelonephritis should be determined by the severity of the infection. In the clinical trial, pediatric patients with moderate to severe infection were initiated on 6 to 10mg/kg IV every 8 hours and allowed to switch to oral therapy (10 to 20mg/kg every 12 hours), at the discretion of the physician.

PEDIATRIC DOSAGE GUIDELINES

Infections	Route of Administration	Dose (mg/kg)	Frequency	Total Duration
Complicated Urinary Tract or Pyelonephritis	Intravenous	6 to 10mg/kg (maximum 400mg per dose; not to be exceeded even in patients weighing > 51kg)	Every 8 hours	10-21 days*
(patients from 1 to 17 years of age)	Oral	10mg/kg to 20mg/kg (maximum 750mg per dose; not to be exceeded even in patients weighing > 51kg)	Every 12 hours	
Inhalational Anthrax (Post-Exposure)**	Intravenous	10mg/kg (maximum 400mg per dose)	Every 12 hours	60 days
	Oral	15mg/kg (maximum 500mg per dose)	Every 12 hours	

* The total duration of therapy for complicated urinary tract infection and pyelonephritis in the clinical trial was determined by the physician. The mean duration of treatment was 11 days (range 10 to 21 days).

** Drug administration should begin as soon as possible after suspected or confirmed exposure to *Bacillus anthracis* spores.
This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.

CONTRAINDICATIONS:
Safety during pregnancy and lactation has not been established.
Ciplet is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or any other quinolones.

WARNINGS:
The use of Ciplet should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with Ciplet should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors, Ciplet should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice. Ciplet should be used with caution in patients with a history of convulsive disorders. Crystalluria related to the use of Ciplet has been observed. Patients receiving Ciplet should be well hydrated and excessive alkalinity of the urine should be avoided.

PRECAUTIONS:
General
Crystals of Ciplet (Ciprofloxacin) have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. Crystalluria related to Ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving Ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.
Central Nervous System
Quinolones, including Ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia.
Renal Impairment
Alteration of the dosage regimen is necessary for patients with impairment of renal function.
Photosensitivity/Phototoxicity
Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions. (e.g., burning, erythema, exudation, 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 after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs.

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

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.
Pregnancy
Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. The Teratogen Information System – concluded that therapeutic doses during pregnancy are unlikely to pose a substantial teratogenic risk.
Nursing Mothers
Ciprofloxacin is excreted in human milk. The amount of ciprofloxacin absorbed by the nursing infant is unknown. Because of the potential for serious adverse reactions in infants nursing from mothers taking ciprofloxacin.
Geriatric Use
Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as Ciplet.

Tendinitis and tendon rupture:
Tendinitis and tendon rupture (especially but not limited to Achilles tendon) sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g., painful swelling, inflammation) the treatment with Ciplet should be discontinued and alternative treatment should be considered. the affected limbs (s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.
Peripheral neuropathy:
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia ,hypaesthesia , dysesthesia, or weakness have been reported in patients receiving quinolones and fluroquinolones. Patients under treatment with Ciplet should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning , tingling, numbness , or weakness develop in order to prevent the development of potentially irreversible condition.

SIDE EFFECTS:
The following side-effects have been observed:
Effects on Gastrointestinal tract:
Nausea, diarrhea, vomiting, dyspepsia, abdominal pain, flatulence, anorexia and oral candidiasis.
Effects on Nervous system*:
Dizziness, headache, tiredness, nervousness, agitation, trembling. Infrequently: insomnia, peripheral paralgesia, sweating, unsteady gait, convulsions, increase in intracranial pressure, anxiety states, nightmares, confusion, depression, hallucinations, in individual cases psychotic reactions.
Reactions on Sensory organs*:
Impaired taste and smell, visual disturbances, tinnitus, transitory impairment of hearing, especially at high frequencies.
Hypersensitivity reactions:
Skin reactions, Interstitial nephritis,
Anaphylactic/anaphylactoid reactions.
Effects on Cardiovascular system:
Tachycardia, hot flushes, migraine and fainting.
Other side effects*:
Joint pain, joint swelling. Very rarely: general feeling of weakness, muscular pains (which may be of special importance in patients with myaesthenia gravis), tendosynovitis, photosensitivity, transient impairment in kidney function including transient kidney failure.
Effects on the blood and blood constituents*:
Eosinophilia, leucocytopenia, granulocytopenia, anaemia, thrombocytopenia. Very rarely: leucocytosis, thrombocytosis, haemolytic anaemia, altered prothrombin values.
Local reactions*:
Phlebitis or thrombophlebitis, local irritation and pain at the site of injection have been reported with intravenous administration of ciprofloxacin.Intravenous infusion should be administered by slow infusion over a period of 60 minutes. These reactions are more frequent if the infusion time is 30 minutes or less, or if small veins of the hand are used. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

*Very rare case of prolonged (up to months or years), disabling and potentialy irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rapture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment in hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

DRUG INTERACTIONS:
Concurrent administration of Ciplet with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half life.

Ciplet Tablets or Ciplet Oral Suspension should be administered 1-2 hours before, or at least 4 hours after taking iron preparations, antacids containing magnesium, aluminium, calcium or sucralfate as interference with absorption may occur. This restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Monitoring of serum creatinine concentrations is advised in patients on concomitant cyclosporine therapy, as transient increases in serum creatinine concentrations have been observed.

The simultaneous administration of Ciplet and warfarin may intensify the action of warfarin. In particular cases, concurrent administration of Ciplet and glibenclamide can intensify the action of glibenclamide (hypoglycaemia). Probenecid interferes with renal secretion of Ciplet. Co-administration of probenecid and Ciplet increases the Ciplet serum concentrations. Metoclopramide accelerates the absorption of Ciplet, resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of Ciplet.
Direction for Preparation (Oral Suspension):
See outer pack for direction for preparation of Ciplet Oral Suspension.

STORAGE CONDITIONS:
See outer pack.

RESENTATION:
- **Ciplet 250mg Tablets:** Pack of 10 film coated tablets.
- **Ciplet 500mg Tablets:** Pack of 10 film coated tablets.
- **Ciplet IV Infusion 200mg/100ml:** Pack of one vial.
- **Ciplet DS IV Infusion 400mg/100ml:** Pack of one vial.
- **Ciplet Oral Suspension 125mg/5ml:** Pack of 60ml bottle.
- **Ciplet Oral Suspension 250mg/5ml:** Pack of 60ml bottle.

Keep all medicines out of the reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
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Karachi-74900, Pakistan.

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