*: 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. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans, reasonably likely to predict clinical benefit.

Conversion of I.V. to Oral Dosing in Adults: Patients whose therapy is started with CIPOX I.V.

Equivalent AUC Dosing Regimens	
Cipox Oral Dosage	Equivalent Cipox I.V. Dosage
250 mg Tablet q 12 h	200 mg I.V.q 12 h
500 mg Tablet q 12 h	400 mg I.V.q 12 h
750 mg Tablet q 12 h	400 mg I.V.q 8 h

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. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. 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 - 500 mg q 12 h
5 - 29	250 - 500 mg q 18 h
Patients on hemodialysis or Peritoneal dialysis	250 - 500 mg q 24 h (after dialysis)

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

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

Women: 0.85 * the value calculated for men.

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.

OVERDOSE and IT'S TREATMENT :
Up to date there have been no reports of intoxication of ciprofloxacin. In cases of overdose gastric lavage is performed, followed by the administration of activated charcoal slurry. Treatment is symptomatic and supportive. No specific antidote for ciprofloxacin is known.
Administration of hemodialysis or peritoneal dialysis can remove only 10 % of ciprofloxacin.

STORAGE :
Store in original package at room temperature below 25°C, keep out of the reach of children.

HOW SUPPLIED :
CIPOX 500 mg Film Tablet, blisters of 14 film-coated tablets

Other Pharmaceutical Dosage Forms Available :
Cipox 250 mg Film Tablet, blisters of 14 film-coated tablets
Cipox 750 mg Film Tablet, blisters of 14 film-coated tablets
Cipox 200 mg / 100 ml I.V. Infusion Solution
Cipox 400 mg / 200 ml I.V. Infusion Solution
Cipox 0.3 % Eye Drops

PRODUCT LICENCE HOLDER :
The holder of trade mark and Marketing Authorization is
"BIOACTIVE T, UNITED KINGDOM.

BioActiveT United Kingdom

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CIPOX 500 mg FILM-COATED TABLET

COMPOSITION : Each film-coated tablet contains: Ciprofloxacin HCl equivalent to 500 mg of Ciprofloxacin.
Pigment: Titanium dioxide.

PHARMACOLOGICAL PROPERTIES :
Pharmacodynamic Properties :
Ciprofloxacin is a synthetic fluoroquinolone derivative with strong bactericid effect. Ciprofloxacin is bactericidal and produces this effect by inhibition bacterial DNA Gyrase (topoisomerase II) enzyme. Ciprofloxacin maintains its bactericidal effect during both stationary and logarithmic growth phase of bacteria. When Ciprofloxacin may administered as a combination with other antibiotics, additive and synergistic behaviour (especially with beta lactamantibiotics) are usually observed.

Microbiology :
Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections (See INDICATIONS)
Aerobic gram-positive microorganisms
Enterococcus faecalis (Many strains are only moderately susceptible.)
Staphylococcus aureus (susceptible to methicillin)
Staphylococcus epidermidis (susceptible to methicillin)
Staphylococcus saprophyticus
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes
Aerobic gram-negative microorganisms
Citrobacter diversus
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris
Providencia stuartii
Providencia rettgeri
Pseudomonas aeruginosa
Serratia marcescens

Ciprofloxacin has been shown to be active against most strains of the following microorganisms; however, the safety and effectiveness of ciprofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.
Aerobic gram-positive microorganisms
Staphylococcus haemolyticus
Staphylococcus hominis
Streptococcus pneumoniae (penicillin-susceptible strains only)
Aerobic gram-negative microorganisms
Acinetobacter iwoffi
Aeromonas hydrophila
Campylobacter jejuni
Edwardsiella tarda
Enterobacter aerogenes
Klebsiella oxytoca
Legionella pneumophila
Neisseria gonorrhoeae
Pasteurella multocida
Salmonella enteritidis
Salmonella typhi
Shigella boydii
Shigella dysenteriae
Shigella flexneri
Shigella sonnei
Vibrio cholerae
Vibrio vulnificus
Yersinia enterocolitica
Most strains of *Burkholderia cepacia* and some strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin, as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.

Pharmacokinetic properties :
Ciprofloxacin is orally well absorbed reaches to maximum plasma levels in 1-1.5 hours. Ciprofloxacin is mainly eliminated by renal excretion. About 55 % of an oral dose and 75 % of an intravenous dose are excreted by the urine. Most of this is eliminated within first 24 hours. Renal elimination is through glomerular filtration and tubular secretion.
About 80 % of Ciprofloxacin is eliminated in unchanged form. It diffuses into all humors and body tissues at therapeutic concentrations. Influence and diffusion of Ciprofloxacin is very important in treatment of infections caused by intracellular pathogens such as Brucella melitensis, Legionella spp., *Chlamydia trachomatis* and *Mycoplasma hominis*.
Following administration of a 750 mg dose of oral ciprofloxacin maximum serum concentration (Cmax) is 4.3 µg/ml, area under curve (AUC) is 20.2 µg.h/ml. Cmax value by oral dose of 750 mg ciprofloxacin is equivalent to Cmax value found following intravenous administration of 400 mg ciprofloxacin.
When ciprofloxacin is administered orally in repeated doses of 750 mg every 12 hours, after the establishment of steady state concentrations Cmax is 3.59 µg/ml and AUC is 31.6 µg/h/ml. AUC values in steady state following repeated administration of 750 mg ciprofloxacin every 12 hours by oral route is equivalent to AUC values obtained after intravenous administration of 400 mg ciprofloxacin every 8 hours as 60-minute infusion.

INDICATIONS :
Ciprofloxacin is indicated for the treatment of infections caused by pathogen bacterium- susceptible to ciprofloxacin listed below.

Adult Patients:
Urinary Tract Infections: caused by Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, methicillin-susceptible Staphylococcus epidermidis, Staphylococcus saprophyticus, or Enterococcus faecalis.
Acute Uncomplicated Cystitis in females: caused by Escherichia coli and Staphylococcus saprophyticus.
Chronic Bacterial Prostatitis: caused by Escherichia coli or Proteus mirabilis.
Lower Respiratory Tract Infections: caused by Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae, and penicillin-susceptible Streptococcus pneumoniae. Also, Moraxella catarrhalis for the treatment of acute exacerbations of chronic bronchitis.

(Note: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or diagnosed pneumonia to Streptococcus pneumoniae.)
Acute Sinusitis: caused by Haemophilus influenzae, penicillin-susceptible Streptococcus pneumoniae, or Moraxella catarrhalis.
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 and Streptococcus pyogenes.
Bone and Joint Infections: caused by Enterobacter cloacae, Serratia marcescens and Pseudomonas aeruginosa.
Complicated Intra-Abdominal Infections (used in combination with metronidazole): caused by Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae, or Bacteroides fragilis.
Infectious Diarrhea: caused by Escherichia coli (enterotoxigenic strains), Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri and Shigella sonnei.
Typhoid Fever: caused by Salmonella typhi.

(Note: The efficacy of ciprofloxacin in the eradication of the typhoid carriers have not been demonstrated.)
Uncomplicated cervical and urethral gonorrhea: Neisseria gonorrhoeae.

Pediatric patients (1 to 17 years of age):
Complicated Urinary Tract Infections and Pyelonephritis: due to Escherichia coli.
(Note: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues.)
Adult and Pediatric Patients:
Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

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. Therapy with CIPRO may be initiated before results of these tests are known.

CONTRAINDICATIONS :
Ciprofloxacin should not be used in patients with hypersensitivity to the quinolone derivatives.

WARNINGS / PRECAUTIONS :
WARNINGS
THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT AND LACTATING WOMEN, PEDIATRIC PATIENTS AND ADOLESCENTS (LESS THAN 18 YEARS OF AGE) HAVE NOT BEEN ESTABLISHED.
In pre-clinical studies, oral administration of ciprofloxacin caused lameness in immature experimental animals. Histopathological examination of the weight-bearing revealed permanent lesions of the cartilage. Other fluoroquinolone compound also produce lesions of cartilage arthropathy in immature animals of various species.

- Convulsions, increased intracranial pressure, and toxic psychosis have been reported during treatment in patients to other quinolones and ciprofloxacin. Ciprofloxacin may also cause dizziness, contusion, tremors, hallucinations and depression. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and treatment methods administered. Ciprofloxacin is used carefully susceptible to convulsion (severe cerebral arteriosclerosis, epilepsy).
- Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline. These reactions have included cardiac arrest, convulsion, status epilepticus, and respiratory failure. This two drugs have avoided to use together. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.
- Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving quinolone therapy. These reactions may occur following the first dose. Oxygen, intravenous steroids, and airway management, including intubation, should be administered as indicated.
- At the time of treatment of ciprofloxacin like occur to all antibiotic Pseudomembranous enterocolitis may be monitoring to depend on reproduction to Clostridium difficile. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile colitis.
- Crystalluria related to ciprofloxacin has been reported in humans because of the alkalinity of the urine. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated.
- Photosensitivity reactions have been observed in patients while receiving some quinolone antibiotics. Direct sunlight should be avoided.
- Ruptures of the Achilles tendon have been reported in patients treated with ciprofloxacin and other quinolones. Ciprofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon.
- Ciprofloxacin should be used with caution in patients with impairment of renal function. Alteration of the dosage regimen is necessary for patients with impairment of renal function. (see DOSAGE AND ADMINISTRATION).
- Periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.
- Superinfections may occur during Ciprofloxacin therapy.Particularly, in patients with enterocolitis, stool culture and susceptibility testing should be performed. Antidiarrheic agents should not be used.
- Ciprofloxacin should be used with caution in geriatric patients because of decreased renal function. Dose adjustment may be required.
- Ciprofloxacin may increase risk of causing Long QT Syndrome or Torsades de Pointes significantly when it administrated with the drugs which may induce Long QT syndrome and Torsades de Pointes. For this reason CIPOX® should not be used with that kind of drugs.

Pregnancy and Nursing Mother: Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless the potential benefit justifies the potential risk to both fetus and mother.

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Nursing Mothers : Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions 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.

Effect on Driving and Operating Machinery : Ciprofloxacin may cause side effects like dizziness, confusion, tremors, hallucinations and agitations in central nervous system. Patients should be warned about this subject.

SIDE EFFECTS / ADVERSE REACTIONS :
The most frequently reported drug related events were nausea (2.5%), diarrhea (1.6%), vomiting (1.0%), abdominal pain (1.7%), headache (1.2%), restlessness (1.1%) and rash (1.0%).
Additional medically important events that occurred in less than 1% of ciprofloxacin patients are listed below.
CARDIOVASCULAR: Palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis.
CENTRAL NERVOUS SYSTEM: dizziness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia.
GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice
MUSCULOSKELETAL: arthralgia, joint stiffness, neck or chest pain, flare up of gout
RENAL/UROGENITAL: interstitial nephritis, nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis
RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism
SKIN/HYPERSENSITIVITY: pruritus, urticaria, photosensitivity, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, allergic reactions may lead to anaphylactic shock.
SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus
Most of the adverse reactions were between mild or moderete degree and were resolved without a treatment by discontinuing of the drug.

Adverse Laboratory Changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship are listed below:

Hepatic- ALT (SGPT), AST (SGOT), alkaline phosphatase, LDH, bilirubin increase.
Hematologic - Eosinophilia, leukopenia, thrombocytopenia, thrombocytosis, pancytopenia.
Renal – Increase in serum creatinine and BUN, crystalluria, cylindruria and hematuria.

IN THE EVENT OF AN UNEXPECTED REACTION CONSULT TO YOUR PHYSICIAN.

DRUG INTERACTIONS :
1) Ciprofloxacin may raise serum concentrations of theophylline and delay its elimination. This may increase theophylline toxicity. Two drugs should not be administered concurrently or serum theophylline concentrations should be monitored. (see WARNINGS / PRECAUTIONS).
2) Ciprofloxacin may also reduce clearance of caffeine and prolong its half life.
3) Ciprofloxacin may cause transient increases in serum creatinine levels in patients undergoing cyclosporine treatment.
4) Fluoroquinolones may potentiate effects of anticoagulants. Prothrombine time should be monitored.
5) Probenecid may increase the plasma level of Ciprofloxacin by blocking its tubular secretion.
6) In some patients who have been using phenytoin and ciprofloxacin concomitantly changes (increase or decrease) in serum phenytoin levels have been reported.
7) Glyburide : Concurrent use of ciprofloxacin and glyburide, an antidiabetic of sulfanylurea class, may result in severe hypoglycemia rarely.
8) Co-administration of ciprofloxacin and magnesium, aluminium and calcium containing antacids, sucralfat, didanosine, or bivalent and trivalent cations such as calcium, iron, or zinc may lower absorption of ciprofloxacin. Ciprofloxacin should be administered at least 2 hours before or 6 hours after.
9) Absorption of ciprofloxacin may be significantly reduced if ciprofloxacin administrated with milk or yogurt.

DOSAGE and ADMINISTRATION :
The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal function and hepatic function.
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. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, or other products containing calcium, iron or zinc.

ADULT DOSAGE GUIDELINES

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