CIPROFLOXACIN

Instructions for the medicinal product

Trade Name: Ciprofloxacin.
International Nonproprietary Name: Ciprofloxacin.
Dosage form: Film-coated tablets.
Composition: Each film coated tablet contains:
Ciprofloxacin Hydrochloride USP eq. to Ciprofloxacin 500 mg.
Pharmacotherapeutic group: Quinolone Antibacterials, fluoroquinolones.
ATC Code: J01MA02.
Pharmacologic property:
Pharmacodynamics:
Ciprofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. In vitro resistance to ciprofloxacin develops slowly by multiple step mutations.
Ciprofloxacin has been shown to be active against most isolates of the following bacteria:
Gram-positive bacteria: *Enterococcus faecalis, Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Streptococcus pneumoniae, Streptococcus pyogenes.*
Gram-negative bacteria: *Campylobacter jejuni, Proteus mirabilis, Citrobacter diversus, Proteus vulgaris, Citrobacter freundii, Providencia rettgeri, Enterobacter cloacae, Providencia stuartii, Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae, Salmonella typhi, Haemophilus parainfluenzae, Serratia marcescens, Klebsiella pneumoniae, Shigella boydii, Moraxella catarrhalis, Shigella dysenteriae, Morganella morganii, Shigella flexneri, Neisseria gonorrhoeae, Shigella sonnei.*
Ciprofloxacin has been shown to be active against *Bacillus anthracis* both in vitro and by use of serum levels as a surrogate marker.
Pharmacokinetics:
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.
Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (Cmax) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.
The absolute bioavailability is approximately 70-80%.
A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.
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. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.
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 for use:
The Ciprofloxacin is indicated for the treatment of the following infections. Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.
Adults:
Lower respiratory tract infections due to Gram-negative bacteria:
- exacerbations of chronic obstructive pulmonary disease;
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis, pneumonia;
- chronic suppurative otitis media;

Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria:
- urinary and genital tract infections;
- gonococcal uretritis and cervicitis due to susceptible Neisseria gonorrhoeae;
- epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae;
- pelvic inflammatory disease including cases due to susceptible Neisseria gonorrhoeae;
- Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea);
- Intra-abdominal infections;
- Infections of the skin and soft tissue caused by Gram-negative bacteria;
- Malignant external otitis;
- Infections of the bones and joints;
- Prophylaxis of invasive infections due to Neisseria meningitidis;
- Inhalation anthrax (post-exposure prophylaxis and curative treatment).
- 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:
- Broncho-pulmonary infections in cystic fibrosis caused by Pseudomonas aeruginosa;
- Complicated urinary tract infections and pyelonephritis;
- Inhalation anthrax (post-exposure prophylaxis and curative treatment);

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.
Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.
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.
Contraindications:
- Hypersensitivity to the active substance or to other quinolones;
- Pediatric patients (less than 18 years of age). The use of Ciprofloxacin in children and adolescents should follow available official guidance;
- Pregnancy and lactation.

With caution. Severe cerebral atherosclerosis, cerebrovascular accidents, mental illness, epilepsy, epileptic syndrome, marked renal and/or hepatic impairment, advanced age.
Dosage and Direction for use:
Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly.
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.
Urinary Tract: acute uncomplicated - 250 mg every 12 hours during 3 days; severe/complicated – 500 mg every 12 hours during 7 to 14 days.
Chronic Bacterial Prostatitis: 500 mg every 12 hours during 28 days.
Lower Respiratory Tract: mild/moderate - 500 mg every 12 hours during 7 to 14 days; severe/complicated - 750 mg every 12 hours during 7 to 14 days.
Acute Sinusitis: 500 mg every 12 hours during 10 days.
Intra-Abdominal: 500 mg every 12 hours during 7 to 14 days.
Infectious Diarrhea: 500 mg every 12 hours during 5 to 7 days.
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.
Pediatrics dosage:
Cystic fibrosis: 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. Total duration of treatment is 10 to 14 days.
Complicated urinary tract infections and pyelonephritis: 10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. Total duration of treatment is 10 to 21 days.
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure: 10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose. Total duration of treatment is 60 days from the confirmation of *Bacillus anthracis* exposure.
Adverse reaction:
Digestive system: nausea, diarrhea, vomiting, abdominal pain, flatulence, loss of appetite, cholestatic jaundice (especially in patients with a history of liver disease), hepatitis, necrosis.
Nervous system disorders: dizziness, headache, fatigue, anxiety, tremors, insomnia, "nightmarish" dream, peripheral paralgesiya (anomaly feelings of pain perception), increased sweating, increased intracranial pressure, confusion, depression, hallucinations, and other manifestations of psychotic reactions (sometimes progressing to the states in which the patient can harm himself), migraine, syncope, thrombosis of the cerebral arteries.
Senses: taste and smell disorders, impaired vision (diplopia, changes in color vision), tinnitus, hearing loss.
CCC: tachycardia, cardiac arrhythmias, blood pressure reduction.
Hematopoietic system: leukopenia, granulocytopenia, anemia, thrombocytopenia, leukocytosis, thrombocytosis and hemolytic anemia. From the laboratory parameters: hypoprothrombinemia, increased activity of "liver" enzymes and alkaline phosphatase, hypercreatininemia, hyperbilirubinemia, hyperglycemia.
Urinary system: hematuria, crystalluria (especially in alkaline urine and low diuresis), glomerulonephritis, dysuria, polyuria, urinary retention, albuminuria, urethral bleeding, hematuria, reduced nitrogen excretory function renal function, interstitial nephritis.
Allergic reactions: itching, rash, blistering, accompanied by bleeding, and the appearance of small nodules that form scabs, drug fever, petechial hemorrhages in the skin (petechiae), swelling of the face or throat, shortness of breath, eosinophilia, increased sensitivity to light, vasculitis, nodular erythema, multiform exudative erythema (including Stevens-Johnson syndrome), toxic epidermal necrolysis (syndrome Layella).
Other: arthralgia, arthritis, tenosynovitis, tendon rupture, fatigue, myalgia, superinfection (candidiasis, pseudomembranous colitis), "tides" of blood to the face.
Overdose:
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.
Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.
Drug Interactions:
Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.
Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.
Tizanidine must not be administered together with ciprofloxacin. There is an increase in serum tizanidine concentration when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.
Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.
Cautions:
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval.
For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking Ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.
Effects on ability to drive and use machines:
Due to its neurological effects, Ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.
Form of the product:
10x1 or 10x10 PVC Blister in a Carton box, with instruction for use.
Storage:
Keep in dry place protected from light at temperature below 30°C. Keep out of reach of children.
Expiration date:
Labeled. Do not use after expiry date.
Distribution Condition:
Prescribed medicine.

Manufactured for:
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