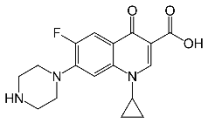
CIPROFLOXACIN TABLETS

Ciprofloxacin HCl USP 500mg

Ciprofloxacin is a fluoroquinolone antibiotic with one fluoro substitution. Its molecular formula is $C_{17}H_{18}FN_3O_3$ and Molecular Weight is 331.3.The chemical structure is:



Mechanism of action

Ciprofloxacin like other fluoroquinolones (FQs) inhibits the enzyme bacterial DNA gyrase that produces cuts in the double-stranded DNA, leading to negative supercoiling and then re-ligation of the cut ends. This helps in averting positive supercoiling which may occur in excess. The DNA gyrase consists of two A and two B subunits: The A subunit brings about cutting of DNA, the B subunit causes negative supercoiling and then the A subunit causes resealing. Ciprofloxacin binds to A subunit with great affinity and restricts the nicking and resealing action. In gram-positive bacteria the major target of action is an analogous enzyme topoisomerase IV which nicks and separates daughter DNA strands once the DNA replication is complete. Ciprofloxacin is more potent against gram positive bacteria due to higher affinity for topoisomerase IV. The damaged DNA leads to formation of exonucleases resulting in digestion of the DNA and this possibly contributes to the bactericidal action of ciprofloxacin.

The mammalian cells possess an enzyme topoisomerase II instead of DNA gyrase or topoisomerase IV that has very low affinity for ciprofloxacin - thus the low toxicity to host cells.

Ciprofloxacin is active against: Gram-positive bacteria, Staphylococcus aureus, Enterococcus faecalis, Staphylococcus epidermidis and saprophyticus, Pneumococci, Streptococcus pyogenes

Gram-negative bacteria: Proteus (vulgaris and mirabilis), Campylobacter, Citrobacter freundii, Providencia (stuartii and rettgeri), E. coli, Klebsiella pneumoniae, Haemophilus influenzae and parainfluenzae, P. aeruginosa, Salmonella typhi, Neisseria gonorrhoeae, Serratia marcescens, Shigella species, Moraxella catarrhalis, Morganella morganii

The prominent microorganism which are resistant are: Bacteroides fragilis, Clostridia, anaerobic cocci.

The noteworthy microbiological features of ciprofloxacin are:

Ciprofloxacin has highly potent action with swift bactericidal action.

Plasmid resistant mutants are not easily selected.

Anaerobes and streptococci present in the intestine which are useful are not affected.

It is effective against the bacteria which are not sensitive to the aminoglycosides and beta lactam group of antibiotics.

The bactericidal action is very less at decreased pH.

Resistance

Resistance is mainly because of chromosomal mutation forming a DNA gyrase or topoisomerase IV which has reduced affinity for ciprofloxacin. Another common mechanism is reduced permeability/increased efflux of ciprofloxacin across bacterial membranes. Like other FQs ciprofloxacin, FQ-resistant mutants are not easily selected hence resistance develops slowly to FQs. However, increasing resistance has been reported among Salmonella, Pseudomonas, staphylococci, gonococci, pneumococci and C. jejuni.

Due to the unique mechanism of action plasmid mediated transferable resistance perhaps does not occur.

A Qnr protein has been seen that offers protection to the DNA gyrase from damage by the FQs. Also modification of ciprofloxacin can be caused by a different type acetyltransferase which is similar to the one which modifies aminoglycoside.

Pharmacokinetics

After oral intake, the FQs have good oral absorption. Food delays absorption. It is extensive tissue distribution. The plasma t1/2 is about 3 to 5 hours. Plasma protein binding is 20-35%. It is excreted primarily in urine, both by glomerular filtration and tubular secretion. Urinary and biliary concentrations are10-50 folds higher than plasma. Plasma concentrations of orally given dose match with those of an IV given dose.

Ciprofloxacin is active against many gram-positive bacteria and gram-negative bacteria. Ciprofloxacin has rapidly bactericidal activity and high potency. Relatively long post-antibiotic effect. Protective intestinal streptococci and anaerobes are spared.

Contra-indications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients
- Concomitant administration of ciprofloxacin and tizanidine

Warnings/Precautions

Rarely crystalluria can be seen in individuals taking ciprofloxacin. Alkalinity of the urine should be avoided in persons taking ciprofloxacin and they should be well hydrated to prevent the formation of highly concentrated urine.

Like other FQs, there are increased chances of inflammation of tendon and even rupture of tendons due to ciprofloxacin.

Like other FQs, ciprofloxacin can lead to deterioration of weakness of muscles in patients of myasthenia gravis.

Hypersensitive reactions can be seen with ciprofloxacin which can be fatal rarely.

Clostridium difficile-associated enterocolitis can be seen with ciprofloxacin.

There are increased chances of arthropathy and tendon rupture has been observed in children.

Rarely large or small sized neurons may be affected by polyneuropathy due to ciprofloxacin leading to altered sensations.
CNS effects like agitative behaviour, decreased sleep, anxiousness and vivid dreams can be seen with ciprofloxacin.
Photosensitive reactions can be seen with ciprofloxacin.
All fluoroquinolones have the potential risk to cause permanent peripheral neuropathy.

Usage in Pregnancy/Lactation
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

Adverse reactions
Side effects are usually mild necessitates withdrawal only in 1.5%. Side effects include nausea, vomiting, bad taste, anorexia, dizziness, headache, restlessness, anxiety, insomnia, rash, pruritus, photosensitivity, urticarial, tendonitis and tendon rupture, hepatic and kidney toxicity.
The commonly observed adverse effects are: GIT: vomiting, altered taste, decreased appetite; CNS: giddiness, headache, anxious behaviour, restlessness, decreased sleep, impairment of concentration, tremor. Seizures are rare; occur only at high doses or when predisposing factors are present.
Other rare reactions are: Hypersensitive: skin rashes, increased itching ,photosensitivity; Tendonitis and tendon rupture; Vasculitis, joint pain , muscle pain; Allergic pneumonitis; Acute kidney insufficiency or failure; Hepatitis; jaundice; acute necrosis of liver or failure; Anemia, including haemolytic and aplastic; decreased platelet count, thrombotic thrombocytopenic purpura; decreased WBC count, agranulocytosis; pancytopenia.

Symptoms of overdose and antidote
An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
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.
Apart from routine emergency measures it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.
Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

Possible drug interactions
Plasma concentration of theophylline, caffeine and warfarin are increased by ciprofloxacin due to inhibition of metabolism: toxicity of these drugs can occur.
NSAIDs may augment the CNS toxicity of ciprofloxacin; seizures are reported.
Antacids, sucralfate and iron salts given concomitantly decrease absorption of FQs.
Concomitant administration of omeprazole reduces plasma concentration of ciprofloxacin.
Both reduced and enhanced serum levels of phenytoin may be seen in persons taking simultaneous Ciprofloxacin.
Concurrent prescription of Ciprofloxacin with glyburide has, rarely can lead to severe hypoglycaemia.
The excretion of ciprofloxacin through the kidney is affected negatively by probenecid leading to enhanced serum levels of ciprofloxacin.
The oral absorption of ciprofloxacin is enhanced by metoclopramide.
Ciprofloxacin increases the serum levels of ropinirole, lidocaine, sildenafil and clozapine.
Excretion of methotrexate by the kidney is inhibited by ciprofloxacin.
Precaution should be taken when using Ciprofloxacin concomitantly with class IA or III antiarrhythmics as Ciprofloxacin may have an additive effect on the QT interval

Indication, Dosage and administration
The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.
Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**

Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intraabdominal infections	Diarrhoea caused by bacterial pathogens including Shigella spp. other than Shigella dysenteriae type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by Shigella dysenteriae type 1	500 mg twice daily	5 days
	Diarrhoea caused by Vibrio cholerae	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to Neisseria meningitides		500 mg as a single dose	1 day (single dose)
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.		500 mg twice daily	60 days from the confirmation of Bacillus anthracis exposure

Children and adolescents

Indications	**Daily dose in mg**	**Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)**
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	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.	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.	60 days from the confirmation of Bacillus anthracis exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients
Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment
Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	**Serum Creatinine [µmol/L]**	**Oral Dose [mg]**
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
<30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration
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. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice).
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Storage: Store below 30°C in a dry place. Keep all medicines out of reach of children

Presentation: 1x10 Tablets in sachet, placed in an outer carton with insert

Manufactured by:

FIDSON

Fidson Healthcare Plc
Km. 38 Lagos Abeokuta Expressway,
Sango Ota, Ogun State.