

Cipesta™

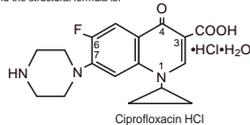
[Ciprofloxacin]

Tablets 250mg, 500mg

Oral Suspension 125mg/5mL, 250mg/5mL

DESCRIPTION

Cipesta (Ciprofloxacin) is a synthetic broad spectrum antimicrobial agent for oral administration. Chemically ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of 1'-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolonecarboxylic acid. The molecular formula is $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ and the structural formula is:



QUALITATIVE AND QUANTITATIVE COMPOSITION

Cipesta (Ciprofloxacin) is available for oral administration as:

Cipesta Tablets 250mg

Each film-coated tablet contains:

Ciprofloxacin HCl USP equivalent to ciprofloxacin...250mg

Cipesta Tablets 500mg

Each film-coated tablet contains:

Ciprofloxacin HCl USP equivalent to ciprofloxacin...500mg

Cipesta Oral Suspension 125mg/5mL

Each reconstituted 5mL contains:

Ciprofloxacin HCl USP equivalent to ciprofloxacin...125mg

Cipesta Oral Suspension 250mg/5mL

Each reconstituted 5mL contains:

Ciprofloxacin HCl USP equivalent to ciprofloxacin...250mg

CLINICAL PHARMACOLOGY

Mechanism of Action

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.

Microbiology

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms.

Aerobic Gram-positive microorganisms

Enterococcus faecalis (Many strains are only moderately susceptible)

Staphylococcus aureus (Methicillin-susceptible strains only)

Staphylococcus epidermidis

Staphylococcus saprophyticus

Streptococcus pneumoniae, *Streptococcus pyogenes*

Aerobic Gram-negative microorganisms

Campylobacter jejuni

Citrobacter diversus

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

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as surrogate marker.

Pharmacokinetics

Absorption

Ciprofloxacin is rapidly and well absorbed from gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism. Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

Distribution

Plasma protein binding ranges from 20-40%. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung, sinuses, inflamed lesions and the urogenital tract where total concentrations exceeding those of plasma concentrations are reached. It appears in the CSF, but concentrations are only about 10% of those in plasma when the meninges are not inflamed. Ciprofloxacin crosses the placenta and is also distributed in breast milk. High concentrations are achieved in bile.

Metabolism

Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Coadministration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs.

Excretion

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300mL/minute, exceeds the normal glomerular filtration rate of 120mL/minute. Thus, active tubular secretion would seem to play a significant role in its elimination. Although bile concentrations of ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 to 2% of the dose is recovered from bile in the form of metabolites. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination. Only small amounts of ciprofloxacin are removed by hemodialysis or peritoneal dialysis.

Special Population

Geriatric Patient

Oral plasma concentrations of ciprofloxacin are higher in elderly (> 65 years) as compared to young adults. Although the C_{max} is increased 16-40%, the increase in mean AUC is approximately 30%, and can be at least partially attributed to decreased renal clearance in the elderly. Elimination half-life is only slightly (~20%) prolonged in the elderly. These differences are not considered clinically significant.

Renal Insufficiency

In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged. Dosage adjustments may be required.

Hepatic Insufficiency

In patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed.

THERAPEUTIC INDICATIONS

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 tract infections
- Genital tract infections
 - gonococcal urethritis 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' diarrhea)
- 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)
- Typhoid fever caused by *Salmonella typhi*.

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.

DOSAGE AND ADMINISTRATION

Cipesta (Ciprofloxacin) can be taken independent of mealtimes. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, didanosine chewable/buffered tablets or pediatric powder for oral solution, other highly buffered drugs, or other products containing calcium, iron or zinc.

Adults:

Cipesta (Ciprofloxacin) 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 susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms and the status of renal function and hepatic function. The dosage range for adults is 100-750mg twice daily. 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.

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

Elderly patients:

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

Children and Adolescents:

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20mg/kg body weight twice daily with a maximum of 750 mg per dose	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10mg/kg body weight twice daily to 20mg/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	10mg/kg body weight twice daily to 15mg/kg body weight twice daily with a maximum of 500 mg per dose	60 days from the confirmation of <i>Bacillus anthracis</i> exposure.
Other severe infections	20mg/kg body weight twice daily with a maximum of 750 mg per dose	According to the type of infections.

Renal Impaired Patients:

The recommended starting and maintenance doses for patients with impaired renal function is given below:

Creatinine Clearance (mL/min/1.73 m ²)	Serum Creatinine (µmol/L)	Oral Dose (mg)
>60	<124	Usual dosage
30-60	124 - 168	250-500mg every 12h
<30	>168	250-500mg every 24h
Patients on hemodialysis	>168	250-500mg every 24h (after dialysis)
Patients on peritoneal dialysis	>168	250-500mg every 24h

Dosing in children with impaired renal and/or hepatic function has not been studied.

Direction for preparation:

Fill previously boiled and cooled water up to the mark on the bottle and shake well. Reconstituted suspension can be used for up to 14 days when stored at 25°C. Shake well before use.

CONTRAINDICATIONS

- Ciprofloxacin is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents or any of the product components.
- Concomitant administration with tizanidine is contraindicated.

ADVERSE REACTIONS

Common

Nausea and diarrhea.

Uncommon

Mycotic superinfections, eosinophilia, decrease appetite, psychomotor hyperactivity / agitation, headache, dizziness, sleep disorders, taste disorders, vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence, increase in transaminases, increased bilirubin, rash, pruritus, urticaria, musculoskeletal pain (e.g. extremely pain, back pain, chest pain), arthralgia, renal impairment, asthenia, fever and increase in blood alkaline phosphatase.

Rare

Antibiotic associated colitis (very rarely with possible fatal outcome), leukopenia, anemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytoma, allergic reaction, allergic edema / angioedema, hyperglycemia, confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideations/thoughts or suicidal attempts and completed suicide), hallucinations, parosmia and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo, visual disturbances (e.g. diplopia), tinnitus, hearing loss / hearing impaired, tachycardia, vasodilatation, hypotension, syncope, dyspnea (including asthmatic condition), hepatic impairment, cholestatic icterus, hepatitis, photosensitivity reactions, myalgia, arthritis, increased muscle tone and cramping, renal failure, hematuria, crystalluria, tubulointerstitial nephritis, edema, sweating (hyperhidrosis) and increased amylase.

PRECAUTIONS

- Hypersensitivity reactions: Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
- CNS disorders: As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction). Ciprofloxacin should be discontinued in patients experiencing symptoms of neurotoxicity in order to prevent the development of an irreversible condition.
- Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.
- Patients with a family history of actual defects in glucose-6-phosphate dehydrogenase activity are prone to hemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.
- Musculoskeletal system: Ciprofloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been excluded. Tendon rupture can occur during or after therapy with quinolones, including ciprofloxacin. Fluoroquinolones may exacerbate muscle weakness in person with myasthenia gravis. Avoid in patients with known history of myasthenia gravis.
- There is a risk of pseudomembranous colitis possibly leading to a fatal outcome. It is important to consider this in patients suffering from severe, persistent diarrhea. If pseudomembranous colitis is suspected treatment with ciprofloxacin should be stopped and appropriate treatment given. Drugs that inhibit peristalsis must not be given.
- Photosensitivity reactions: Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e., sunburn-like skin reactions) occur.
- Peripheral neuropathy: Ciprofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness and/or weakness or is found to have deficits in light touch, pain, temperature, position sense, vibratory sensation and/or motor strength in order to prevent the development of an irreversible condition.
- Syphilis: Antimicrobial agents used in high dose for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with ciprofloxacin should have a follow-up serologic test for syphilis after 3 months.
- Cardiac disorders: Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
 - congenital long QT syndrome
 - concomitant use of drugs that are known to prolong the QT interval (e.g. class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
 - uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
 - cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.
- Hepatobiliary system: Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Pregnancy

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.

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.

Drug Interactions

Cytochrome P450 (CYP450): Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g., theophylline, clozapine, tacrine, ropinirole, tizanidine, duloxetine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations, especially of theophylline, may be necessary.

Chelation complex formulation: Ciprofloxacin should be administered at least 2 hours before or 6 hours after multivalent cationic drugs and mineral supplements (e.g., calcium, magnesium, aluminum or iron), polymeric

phosphate binders (e.g., sevelamer), succralfate or antacids and highly buffered drugs (e.g., didanosine) as interference with absorption may occur. When appropriate, patients should be advised not to self-medicate with preparations containing these compounds during therapy with ciprofloxacin. This restriction does not apply to the class of H₂ receptor blocker drugs.

Theophylline: Serious and fatal reactions have been reported in patients receiving concurrent administration of ciprofloxacin and theophylline. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Other xanthine derivatives: Raised serum concentrations of caffeine or pentoxifylline (oxpentifylline) were reported on concurrent administration of these xanthine derivatives.

Phenytoin: Phenytoin levels may be altered when ciprofloxacin is used concomitantly.

Glyburide/Glibenclamide: The concomitant administration of ciprofloxacin with the sulfonylurea glyburide and glibenclamide has on rare occasions, resulted in severe hypoglycemia.

Warfarin: Quinolones, including ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid: Probenecid interferes with renal tubular secretion of ciprofloxacin and produces and increase in the level of ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide: Metoclopramide significantly accelerates the absorption of oral ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of ciprofloxacin.

NSAIDs: Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions.

Food and Dairy Products: The concurrent administration of dairy products or mineral fortified drinks alone (e.g., milk, yogurt, calcium fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

Omeprazole: Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Cyclosporin: A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin were administered simultaneously. Therefore, it is necessary to monitor the serum creatinine concentrations in these patients frequently (twice a week).

Sildenafil: Upon concomitant administration of an oral dose of 50mg Sildenafil with 500mg ciprofloxacin, C_{max} and AUC of sildenafil were increased approximately twofold. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

OVERDOSAGE

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment, including monitoring of renal function (including urinary pH and acidity, if required, to prevent crystalluria) and administration of magnesium, aluminum, or calcium containing antacids which can reduce the absorption of ciprofloxacin. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

STORAGE

Store at 25°C (Excursions permitted between 15°C - 30°C). Protect from sunlight and moisture.

HOW SUPPLIED

Cipesta (Ciprofloxacin) Tablets 250mg are available in pack of 10's.
Cipesta (Ciprofloxacin) Tablets 500mg are available in pack of 10's.
Cipesta (Ciprofloxacin) Oral Suspension 125mg/5mL are available in pack of 60mL.
Cipesta (Ciprofloxacin) Oral Suspension 250mg/5mL are available in pack of 60mL.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

 **Getz**
pharma
(PVT) LIMITED
www.getzpharma.com 29-30/27,
K.I.A., Karachi,
Pakistan

L-20008106