GETCIPRO™

[CIPROFLOXACIN]

℞ Prescription drug

DESCRIPTION

GETCIPRO (Ciprofloxacin hydrochloride) Tablets is a synthetic broad spectrum antimicrobial agent for oral administration.

Chemically ciprofloxacin hydrochloride, a fluoroquinolone, is the monohydrochloride monohydrate salt of1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The molecular formula is $C_{17}H_{18}FN_3O_3$-HCl-H_2O and its structural formula is:

COMPOSITION

Each film-coated tablet contains

Active ingredient: Ciprofloxacin HCl USP equivalent to ciprofloxacin …250mg

Inactive ingredients: Microcrystalline Cellulose (Avicel PH-102), Povidone (K-30), Cross Povidone (Colloidal Anhydrous Silica (Aerosil 200), Magnesium Stearate, Hydroxy propyl methyl cellulose (Methocel), Titanium Dioxide, P.E.G 6000, Purified Talc

Each film-coated tablet contains

Active ingredient: Ciprofloxacin HCl USP equivalent to ciprofloxacin …500mg

Inactive ingredients: Microcrystalline Cellulose (Avicel PH-102), Povidone (K-30), Cross Povidone (Colloidal Anhydrous Silica (Aerosil 200), Magnesium Stearate, Hydroxy propyl methyl cellulose (Methocel), Titanium Dioxide, P.E.G 6000, Purified Talc

Each film-coated tablet contains

Active ingredient: Ciprofloxacin HCl USP equivalent to ciprofloxacin …750mg

Inactive ingredients: Microcrystalline Cellulose (Avicel PH-102), Corn Starch, Povidone (K-30), Crospovidone, Colloidal Anhydrous Silica (Aerosil 200), Magnesium Stearate, Instacoat Aqua III Pink D-3117, Purified Talc

CLINICAL PHARMACOLOGY

Mechanism of Action

Ciprofloxacin is a synthetic 4-quinolone derivative, with bactericidal activity. It acts via inhibition of bacterial DNA gyrase (topoisomerase, which is essential in the reproduction of bacterial DNA), ultimately resulting in interference with DNA function. Ciprofloxacin is highly active against a wide range of Gram-positive and Gram-negative organisms and has shown activity against some anaerobes.

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
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

When ciprofloxacin is given concomitantly with food, there is a delay in the absorption of the drug, resulting in peak concentrations that occur closer to 2 hours after dosing rather then 1 hour. The overall absorption of ciprofloxacin is not substantially affected.

Effect of Food

The intake of food at the same time as administration of oral ciprofloxacin has a marginal but clinically not relevant effect on the pharmacokinetic parameters C_{max} and AUC. No specific recommendations are necessary with regard to time of administration of oral ciprofloxacin relative to food intake.

Distribution

Plasma protein binding ranges from 20-40%. Ciprofloxacin is widely distributed in the body and tissue penetration is generally good. 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 to 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 the 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 subjects (> 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.

INDICATIONS

GETCIPRO (Ciprofloxacin) is indicated for the treatment of the following infections caused by sensitive bacteria:

Adults

Respiratory tract infections: e.g., lobar and bronchopneumonia, acute and chronic bronchitis, acute exacerbation of cystic fibrosis, bronchiectasis, empyema. Ciprofloxacin is not recommended as first-line therapy for the treatment of pneumococcal pneumonia.

Ciprofloxacin may be used for treating Gram-negative pneumonia.

Ear, nose and throat infections: e.g., mastoiditis, otitis media and sinusitis, especially if due to Gram-negative bacteria (including Pseudomonas spp.). Ciprofloxacin is not recommended for the treatment of acute tonsillitis.

Urinary tract infections: e.g., uncomplicated and complicated urethritis, acute uncomplicated cystitis, pyelonephritis, chronic bacterial prostatitis, epididymitis.

Skin and soft tissue infections: e.g., infected ulcers, wound infections, abscesses, cellulitis, otitis externa, erysipelas, infected burns.

Bone and joint infections: e.g., osteomyelitis, septic arthritis.

Complicated Intra-abdominal infections: e.g., peritonitis, intra-abdominal abscesses. Infections of the biliary tract: e.g., cholangitis, cholecystitis, empyema of the gall bladder. Gastro-intestinal infections: e.g., enteric fever (typhoid fever), infective diarrhea. Pelvic infections: e.g., salpingitis, endometritis, pelvic inflammatory disease. Severe systemic infections: e.g., septicaemia, bacteraemia, peritonitis, infections in immuno-suppressed patients.

Gonorrhea: including urethral, rectal and pharyngeal gonorrhea caused by -lactamase producing organisms or organisms moderately sensitive to penicillin.

GETCIPRO (Ciprofloxacin) is also used for the prophylactic treatment against:

1. Infection in elective upper gastro-intestinal tract surgery and endoscopic procedures, where there is an increased risk of infection.
2. Meningococcal meningitis

Children and adolescents

Ciprofloxacin may be used for the 2nd and 3rd line treatment of complicated urinary tract infections and pyelonephritis in children and adolescents 1-17 years of age and for the treatment of acute pulmonary exacerbation of cystic fibrosis associated with P.aruginosa infection in children and adolescents aged 5-17 years of age.

Inhalation Anthrax in Adults and Children

To reduce the incidence or progression of disease following confirmed or suspected exposure to aerosolized Bacillus anthracis.

DOSAGE AND ADMINISTRATION

GETCIPRO (Ciprofloxacin) tablets 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

GETCIPRO (Ciprofloxacin) tablets 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.

Indication	Severity	Dosage (mg Ciprofloxacin)	Frequency	Duration of treatment (Days)***
Urinary Tract	Acute uncomplicated mild/moderate Severe/complicated	250mg 250mg 500mg	q 12 hr q 12 hr q 12 hr	3 7 - 14 7 - 14
Chronic bacterial protatitis	Mild/moderate	500mg	q 12 hr	28
Lower respiratory tract*	Mild/moderate Severe/complicated	500mg 750mg	q 12 hr q 12 hr	7 - 14 7 - 14
Acute Sinusitis	Mild/moderate	500mg	q 12 hr	10
Skin and skin Sturcture	Mild/moderate Severe/complicated	500mg 750mg	q 12 hr q 12 hr	7 - 14 7 - 14
Bone and joint	Mild/moderate Severe/complicated	500mg 750mg	q 12 hr q 12 hr	≥4-6 weeks ≥4-6 weeks
Intra-abdominal**	Complicated	500mg	q 12 hr	7 - 14
Infectious diarrhea	Mild/moderate/ Severe	500mg	q 12 hr	5 - 7
Typhoid fever	Mild/moderate	500mg	q 12 hr	10
Urethral and cervical gonococcal infections	Uncomplicated	250mg	Single dose	Single dose
Inhalational anthrax (post-exposure)		500mg	q 12 hr	60
Prophylaxis Elective upper gastro-intestinal surgical and endoscopic		750mg single dose 60-90 minutes prior to the procedure		
Meningococcal meningitis		500mg	Single dose	Single dose

*Although the pharmacokinetics of ciprofloxacin remains unchanged in patients with cystic fibrosis, the low body weight of these patients should be taken into consideration when determining dosage.

**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).

Children and adolescents
Cystic fibrosis
The recommended dosage of ciprofloxacin in pediatric cystic fibrosis patients with acute pulmonary exacerbations associated with P. aeruginosa infection, at a dose of 20mg/kg orally twice daily (maximum daily dose 1500mg). The duration of treatment is 10-14 days.
Complicated urinary tract infections and pyelonephritis
For complicated urinary tract infections or pyelonephritis the dose is 10 to 20mg/kg orally every 12 hours with a maximum of 750mg per dose not to be exceeded even in patients weighing >51kg. The duration of treatment is 10-21 days.
Inhalation anthrax
The recommended dose of ciprofloxacin in pediatric patients is 15mg/kg orally twice daily (maximum daily dose of 1000mg). The treatment should begin as soon as possible after confirmed or suspected exposure and should continue for 60 days.
Impaired Renal Function
The dosing for renally impaired adult patients is given below:

Creatinine Clearance (mL/min)	Dose	Frequency
<50	Usual Dosage	
30 - 50	250mg-500mg	q 12 h
5 - 29	250mg-500mg	q 18 h
Patients on hemodialysis or pentoneal dialysis	250mg-500mg	q 24 h (after dialysis)

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
Ciprofloxacin is generally well tolerated.
The side effects often involve the gastrointestinal tract, CNS or skin.
Gastrointestinal disturbances include nausea, vomiting, diarrhea, abdominal pain and dyspepsia are the most frequent adverse effects. Pseudomembranous colitis has been reported rarely. CNS disturbances include headache, dizziness and restlessness are among the commonest side effects. Others include tremor, drowsiness, insomnia, nightmares and visual and other sensory disturbances and more rarely, hallucinations, psychotic reactions, depression and convulsions. Paraesthesia and peripheral neuropathy have occurred occasionally.
Hypersensitivity-type reactions include rash and pruritus. In addition, rarely, vasculitis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity and anaphylaxis.
Musculoskeletal reactions include reversible arthralgia and joint erosions. Tendon damage has been reported.
Hematological disturbances include eosinophilia, leucopenia, thrombocytopenia and very rarely pancytopenia, hemolytic anemia or agranulocytosis, myalgia, gynecomastia and lymphadenopathy. Cardiovascular effects include tachycardia, oedema, syncope, hot flushes and sweating. Side effects involving the special senses include disturbed vision, tinnitus, hearing loss and bad taste.
Other adverse effects include transient increases in serum creatinine or blood urea nitrogen and occasionally, acute renal failure secondary to interstitial nephritis; crystalluria; elevated liver enzyme values, jaundice and hepatitis.
In children, arthropathy is reported to occur commonly. It should be expected that events reported in adults may also occur in pediatric patients.
WARNINGS

Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

PRECAUTIONS
- Hypersensitivity reactions: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving quinolone therapy. The drug should be discontinued immediately at the first appearance of a skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted
- 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).
- 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.
- Tendon effects: 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.
- 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.

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.
Effects on ability to drive and use machines
Ciprofloxacin can alter the capacity for reactions to an extent that impairs the ability to drive a vehicle, to operate machinery or to work safely even when used as prescribed. This applies to a greater degree at the start of treatment, when the dose is increased, and when switching medication, as well as in conjunction with alcohol.
Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.
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), sucralfate 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.
Phenytoin: Phenytoin levels may be altered when ciprofloxacin is used concomitantly.
Glyburide/Glibenclimide: The concomitant administration of ciprofloxacin with the sulfonylurea glyburide and glibenclimide 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.
Probencid: Probencid 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, yougurt, 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 Cmax 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).
Inform doctors with side effects when using medicine
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 acidify, 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 below 30°C. Protect from sunlight and moisture.

SHELF-LIFE:24 months from the manufacturing date
HOW SUPPLIED
GETCIPRO (Ciprofloxacin) 250mg: Box of 2 blisters x 10's.
GETCIPRO (Ciprofloxacin) 500mg: Box of 2 blisters x 10's.
GETCIPRO (Ciprofloxacin) 750mg: Box of 2 blisters x 10's.
SPECIFICATION: USP
WARNING:
- **Read carefully the leaflet before use.**
- **For further information, please contact your doctor.**
- **This drug is dispensed on prescription only.**
- **Keep out of reach of children.**

Manufactured by:

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

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