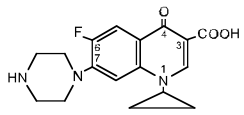
Cipesta™ XR

[Ciprofloxacin]

سِپسٹا ایکس آر

Extended-Release Tablets
500mg and 1000mg

DESCRIPTION
CIPESTA XR contains ciprofloxacin, a synthetic broad spectrum anti-microbial agent for oral administration. Chemically, it is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. The molecular formula is $C_{17}H_{18}FN_3O_3$ and structural formula is:



Ciprofloxacin

QUALITATIVE AND QUANTITATIVE COMPOSITION
CIPESTA XR (Ciprofloxacin) Tablets are available for oral administration as:

CIPESTA XR Tablets 500mg
Each extended-release tablet contains:
Ciprofloxacin USP… 500mg

CIPESTA XR Tablets 1000mg
Each extended-release tablet contains:
Ciprofloxacin USP… 1000mg

CLINICAL PHARMACOLOGY

Mechanism of Action
The bactericidal action of ciprofloxacin results from the inhibition of bacterial type II topoisomerase (DNA-gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

MICROBIOLOGY
Ciprofloxacin has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections as indicated.

Gram-positive bacteria
Enterococcus faecalis (Vancomycin-susceptible isolates only)
Staphylococcus saprophyticus

Gram-negative bacteria
Escherichia coli
Klebsiella pneumoniae
Proteus mirabilis
Pseudomonas aeruginosa

Pharmacokinetics
Absorption
Following oral administration of ciprofloxacin extended-release tablets, ciprofloxacin is rapidly and almost completely absorbed. The area under the plasma concentration time curve (AUC) following a single dose of ciprofloxacin 500mg and 1000mg is 7.24mg.h/L and 15.3 mg.h/L respectively. Maximum plasma concentrations of 1.42 mg/L and 2.70 mg/L are attained between 1 and 4 hours after dosing of Ciprofloxacin 500mg and 1000mg respectively.

Distribution
The protein binding of ciprofloxacin is low (20%-30%) and the substance is present in plasma largely in a non-ionized form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state distribution volume of 2-3L/kg body weight shows that ciprofloxacin penetrates in tissues resulting in concentrations which clearly exceeds the corresponding serum levels.

Metabolism
Four metabolites of ciprofloxacin have been identified in human urine. The metabolites have antimicrobial activity, but are less active than unchanged ciprofloxacin.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, non-renally. The urinary excretion of ciprofloxacin is almost complete within 24 hours after 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 matabolites.

Special Population
Elderly
Plasma concentrations of ciprofloxacin are higher in elderly subjects (> 65 years) as compared to young adults. Elimination half-life is only slightly (~20%) prolonged in the elderly.

Patients with Renal Impairment
In patients with reduced renal function, the half-life of ciprofloxacin is slightly prolonged.

THERAPEUTIC INDICATIONS
CIPESTA XR (Ciprofloxacin) is indicated only for the treatment of following urinary tract infections, caused by susceptible isolates of designated microorganisms:

- Uncomplicated Urinary Tract Infections (Acute Cystitis)
- Complicated Urinary Tract Infections
- Acute Uncomplicated Pyelonephritis

DOSAGE AND ADMINISTRATION
CIPESTA XR (Ciprofloxacin) Tablets should be administered orally once daily as described in the following dosage guidelines table:

Dosage Guidelines

Indication	Unit Dose	Frequency	Usual Duration
Uncomplicated Urinary Tract Infection (Acute Cystitis)	500mg	Q24h	3 Days
Complicated Urinary Tract Infection	1000mg	Q24h	7-14 Days
Acute Uncomplicated Pyelonephritis	1000mg	Q24h	7-14 Days

CIPESTA XR (Ciprofloxacin) Tablets can be taken independently of the mealtimes.

Special Population
Impaired Renal Function
No dosage adjustment is required for patients with uncomplicated urinary tract infections receiving CIPESTA XR (Ciprofloxacin) Tablets 500mg. In patients with complicated urinary tract infections and acute uncomplicated pyelonephritis, who have a creatinine clearance of < 30 mL/min, the dose of CIPESTA XR (Ciprofloxacin) Tablets should be reduced from 1000mg to 500mg daily. For patients on hemodialysis or peritoneal dialysis, administer CIPESTA XR (Ciprofloxacin) after the dialysis procedure is completed (maximum dose should be CIPESTA XR 500mg Q 24 h).

Children and Adolescents
The use of ciprofloxacin extended-release tablets is not recommended in patients less than 18 years of age.

CONTRAINDICATIONS
Ciprofloxacin is contraindicated:
- In patients with hypersensitivity to ciprofloxacin, any member of the quinolone class of antiomicrobial agents, or any of the product components.
- To used concomitantly with tizanidine.

ADVERSE REACTIONS
Common:
Nausea and diarrhea.

Uncommon:
Mycotic superinfections, eosinophilia, anorexia, psychomotor hyperactivity/agitation, headache, dizziness, sleep disorder, taste disorder, vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence, increase in serum transaminases, increased bilirubin, rash, urticaria, pruritis, arthralgia, renal impairment, unspecific pain, feeling unwell, fever and increase in blood alkaline phosphatase.

Rare:
Antibiotic associated colitis (very rarely with possible fatal outcome), leucopenia, anemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytemia, allergic reactions, allergic oedema/angiooedema, hyperglycemia, confusion, disorientation, anxiety reaction, abnormal dreams, depression, hallucinations, par and dysaesthesia, hypoaesthesia, tremor, seizures, vertigo, visual disturbance, tinnitus, hearing loss, tachycardia, vasodilatation, hypotension, syncope, dyspnea (including asthmatic condition), hepatic impairment, jaundice, hepatitis (non infective), photosensitivity reactions, unspecific blistering, myalgia, arthritis, renal failure, increased muscle tone and cramping, hematuria, crystalluria, tubulointerstitial nephritis, oedema, sweating (hyperhidrosis), abnormal prothrombin time and increased amylase.

Very Rare:
Hemolytic anemia, agranulocytosis, pancytopenia (life threatening), bone marrow depression (life threatening), anaphylactic reaction, anaphylactic shock (life threatening), serum sickness like reaction, psychotic reactions, migraine, disturbed coordination, smell disorders, hyperesthesia, intracranial hypertension, visual colour distortions, hearing impairment, vasculitis, pancreatitis, liver necrosis (very rarely progressing to life threatening liver failure), petechiae, erythema, multiform erythema nodosum, stevens-johnson syndrome (potentially life threatening), toxic epidermal necrolysis (potentially life threatening), muscular weakness, tendonitis, tendon rupture (predominantly achilles tendon), exacerbation of symptoms of myasthenia gravis and gait disturbance.

PRECAUTIONS
Tendinopathy and Tendon Rupture
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 patient with kidney, heart or lung transplants. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of tendon.

Exacerbation of Myasthenia Gravis
Fluoroquinolones, including ciprofloxacin may exacerbate muscle weakness in person with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis.

Hypersensitivity
Ciprofloxacin may be associated with hypersensitivity reactions, ciprofloxacin should be discontinued at the first sign of a skin rash or other allergic reaction.

Clostridium difficile associated diarrhea (CDAD)
CDAD has been reported with use of nearly all antibacterial agents, including ciprofloxacin, and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued.

Crystalluria
Crystalluria related to ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving ciprofloxacin.

Photosensitivity/Phototoxicity
Moderate to severe Photosensitivity/Phototoxicity reaction can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs.

Cardiac disorders
Ciprofloxacin is associated with the cases of QT prolongation. In general, elderly patients may be more susceptible to drug associated effects on the QT interval.

CNS effects
Ciprofloxacin should be used with caution in epileptic patients and patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold.

Hepatobiliary System
Cases of severe hepatotoxicity, including hepatic necrosis, life-threatening hepatic failure and fatal events have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatitis treatment should be discontinued immediately.

Peripheral Neuropathy
If the patient experience symptoms of neuropathy ciprofloxacin should be discontinued.

Interaction with tests
Ciprofloxacin *in vitro* may interfere with the *Mycobacterium spp.* culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Ciprofloxacin should not be used during pregnancy unless 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, 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
Ciprofloxacin is an inhibitor of the hepatic CYP1A2 enzyme pathway. Coadministration of ciprofloxacin and other drugs primarily metabolized by CYP1A2 (for example, theophylline, methylxanthines, caffeine, tizanidine, ropinirole, clozapine, olanzapine) results in increased plasma concentrations of the coadministered drug.

Drugs known to prolong QT interval
Precaution should be taken when using ciprofloxacin concomitantly with drugs known to prolong the QT interval (for example, class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) as ciprofloxacin may have an additive effect on the QT interval.

Chelation complex formation
The simultaneous administration of ciprofloxacin and multivalent cation-containing medicinal products and mineral supplements (e.g., calcium, magnesium, aluminum, iron), polymeric phosphate binders (e.g., sevelamer, lanthanum carbonate), sucralfate or antacids and highly buffered drugs (e.g., didanosine), containing magnesium, aluminum or calcium reduce the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before, or at least 4 hours after these preparations.

Food and dairy product
The concurrent administration of dairy products or mineral-fortified drinks alone (e.g., milk, yoghurt, calcium fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

Phenytoin
Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant ciprofloxacin. Monitoring of phenytoin serum concentration measurements is recommended during and shortly after coadministration of ciprofloxacin with phenytoin.

Probenecid
Probenecid interferes with renal secretion of ciprofloxacin. Coadministration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

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

Theophylline
Concurrent administration of ciprofloxacin with theophylline may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), elevated serum concentrations of these xanthine derivatives have been reported.

Methotrexate
Patients under methotrexate therapies should be carefully monitored when concomitant ciprofloxacin therapy is indicated, since this combination leads to increase plasma levels of methotrexate.

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

Vitamin K antagonists
Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The INR should be monitored frequently during and shortly after coadministration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Glibenclamide
Concurrent administration of ciprofloxacin and glibenclamide can intensify the action of glibenclamide.

Ropinirole
Concomitant use of ropinirole with ciprofloxacin, results in an increase of C_{max} and AUC of ropinirole. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after coadministration with ciprofloxacin.

Clozapine
Concomitant administration of ciprofloxacin with clozapine increase serum concentrations of clozapine and N-desmethylclozapine. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised.

Sildenafil
Concomitant administration of ciprofloxacin with sildenafil increase C_{max} and AUC of sildenafil approximately twofolds. Therefore, caution should be used when prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

OVERDOSAGE
Symptoms
In the event of acute excessive overdosage, reversible renal toxicity has been reported in some cases.

Treatment
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, urinary pH and acidify, if required, to prevent crystalluria and administration of magnesium 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 to 30°C).
Protect from sunlight and moisture.
The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

CIPESTA XR (Ciprofloxacin) Tablets 500mg is available in blister pack of 10's.

CIPESTA XR (Ciprofloxacin) Tablets 1000mg is available in blister pack of 10's.

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.

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