Cipesta™
[Ciprofloxacin]

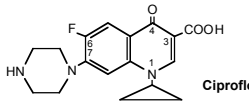
Cipesta™ DS
[Ciprofloxacin]

سِپسّٹا

سِپسّٹا ڈی ایس

200mg/100mL
400mg/100mL
IV Infusion

DESCRIPTION
Cipesta IV contains ciprofloxacin which is a synthetic broad-spectrum antimicrobial agent for intravenous administration. Ciprofloxacin, a fluoroquinilone, 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 its chemical structure is:



Ciprofloxacin

QUALITATIVE AND QUANTITATIVE COMPOSITION
Cipesta IV (Ciprofloxacin) Infusion is available as:

Cipesta IV Infusion 200mg/100mL
Each mL of solution for infusion contains:
Ciprofloxacin USP…2mg (as ciprofloxacin lactate)

Cipesta DS IV Infusion 400mg/100mL
Each mL of solution for infusion contains:
Ciprofloxacin USP…4mg (as ciprofloxacin lactate)

CLINICAL PHARMACOLOGY
Mechanism of Action
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, 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 micro-organisms.

Commonly susceptible species
Aerobic Gram-positive micro-organisms
Bacillus anthracis

Aerobic Gram-negative micro-organisms
Aeromonas spp., Brucella spp., Citrobacter koseri, Francisella tularensis Haemophilus ducreyi, Haemophilus influenzae, Legionella spp., Moraxella catarrhalis, Neisseria meningitides, Pasteurella spp., Salmonella spp., Shigella spp., Vibrio spp., Yersinia pestis.

Anaerobic micro-organisms
Mobiluncus

Other micro-organisms
Chlamydia trachomatis, Chlamydia pneumoniae, Mycoplasma hominis, Mycoplasma pneumoniae.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms
Enterococcus faecalis, Staphylococcus spp.

Aerobic Gram-negative micro-organisms
Acinetobacter baumannii, Burkholderia cepacia, Campylobacter spp., Citrobacter freundii Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia spp., Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens.

Anaerobic micro-organisms
Peptostreptococcus spp., Propionibacterium acnes

Pharmacokinetics
Absorption
Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over thedose range of up to 400mg administered intravenously. Comparison of the pharmacokinetic parameters for twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

Distribution
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 2-3L/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.

Metabolism
Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Excretion
Ciprofloxacin is largely excreted unchaged both renallyand, to a smaller extent, fecally Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

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

THERAPEUTIC INDICATIONS:
Cipesta IV (Ciprofloxacin) is indicated for the treatment of the following infections caused by bacteria sensitive to Ciprofloxacin:

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 exacerbationof chronicsinusitisespecially if these arecaused by Gram-negative bacteria
- Urinary tract infections
- Genital tract infections
  - -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
- 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* in children and adolescents aged 5-17 years
- Complicated urinary tract infections and pyelonephritis in children and adolescents aged 1-17 years
- 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.

DOSAGE AND ADMINISTRATION
Cipesta IV (Ciprofloxacin) should be administered by intravenous infusion. The dosage is determined bythe indication, theseverity and the siteof the infection,the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and by the body weight in children and adolescents. The duration of treatment depends on the severity of the illness and on the clinical and bacterial course. After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.
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 (including switch to oral therapy as soon as possible)
Infections of the lower respiratory tract		400mg twice daily to 400mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400mg twice daily to 400mg three times a day	7 to 14 days
	Chronic suppurative otitis media	400mg twice daily to 400mg three times a day	7 to 14 days
	Malignant external otitis	400mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400mg twice daily to 400mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400mg twice daily to 400mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400mg twice daily to 400mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhea	400mg twice daily	1 day
	Diarrhea caused by *Shigella dysenteriae* type 1	400mg twice daily	5 days
	Diarrhea caused by *Vibrio cholerae*	400mg twice daily	3 days
	Typhoid fever	400mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400mg twice daily to 400mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400mg twice daily to 400mg three times a day	7 to 14 days
Bone and joint infections		400mg twice daily to 400mg three times a day	max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance with official guidance.		400mg twice daily to 400mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment. Drug administration should begin as soon as possible after suspected or confirmed exposure.		400mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and Adolescents:

Indications	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10mg/kg body weight three times a day maximum of 400mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6mg/kg body weight three times a day to 10mg/kg body weight three times a day with a maximum of 400mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment. 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 400mg per dose.	60 days from the confirmation of *Bacillis anthracis* exposure.
Other severe infections	10mg/kg body weight three times a day with a maximum of 400mg per dose.	According to the type of infections.

Renal Impaired Patients:
The recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance (mL/min/1.73 m^2)	Serum Creatinine (µmol/L)	Intravenous Dose (mg)
>60	<124	Usual dosage
30-60	124 to 168	200-400mg every 12h
<30	>169	200-400mg every 24h
Patients on hemodialysis	>169	200-400mg every 24h (after dialysis)
Patients on peritoneal dialysis	>169	200-400mg every 24h.

Method of administration:
Cipesta IV (Ciprofloxacin) Infusion should be checked visually prior to use. It must not be used if cloudy. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400mg and 30 minutes for 200mg. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation.

CONTRAINDICATION
- Ciprofloxacin is contraindicated in patients with hypersensitivity to ciprofloxacin, other quinolone or any of the product components.
- Concomitant administration with tizanidine is contraindicated.

ADVERSE REACTIONS
Ciprofloxacin is generally well tolerated. Most of the adverse events reported were described as only mild or moderate in severity and abated soon after the drug was discontinued and required no treatment.

Common: Nausea, diarrhea, infusion site reactions.

Uncommon: Mycotic superinfections, eosinophilia, anorexia, 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., extremity pain, back pain, chest pain), arthralgia, renal impairment, asthenia, fever, increase in blood alkaline phosphatase.

Rare: Antibiotic associated colitis (very rarely with possible fatal outcome), leukopenia, anemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytemia, allergic reaction allergic oedemia/angioedema, hyperglycemia, confusion and disorientation, anxiety reaction, abnormal dreams, depression, hallucinations, paresthesia and dysesthesia, hypoesthesia, tremor, seizures,vertigo, visual disturbances, tinitus, hearing loss/hearing impairment tachycardia, vasodilatation, hypotension, syncope, dyspnea (including asthmatic condition), hepatic impairment, cholestatic icterus, hepatitis, photosensitivity reactions, myalgia, arthritis, increased muscletone and cramping, renal failure, hematuria, crystalluria, tubulointerstitial nephritis, oedema, sweating (hyperhidrosis), abnormal prothrombin level, 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, gait disturbance, olfactory nerve disorders, intracranial hypertension, visual colour distortions, vasculitis, pancreatitis, liver necrosis (very rarely progressing to life-threatening hepatic failure), petechiae, erythema multforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal, necrolysis (potentially life-threatening), muscular weakness, tendinitis, tendon rupture (predominantly Achilles tendon), exacerbation of symptoms of myasthenia gravis.

Precaution
Musculoskeletal System
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. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon.
Fluoroquinolones, including Ciprofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Ciprofloxacin in patients with known history of myasthenia gravis.

Genital tract infections
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.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.

Hypersensitivity
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.

Photosensitivity
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.

Central nervous system
Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued.

Peripheral neuropathy
Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

Cardiac disorders
Caution should be taken when using ciprofloxacin in patients with known risk factors for prolongation of the QT interval. Elderly patients and women may be more sensitive to QTc-prolonging medications.Therefore, caution should be taken when usingciprofloxacin in these populations.

Gastrointestinal system
Clostridium difficile associated diarrhea (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.

Renal and urinary system
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.

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.

Glucose-6-phosphate dehydrogenase deficiency
Ciprofloxacin should be avoided in patients with glucose-6-phosphate dehydrogenase deficiency, unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Injection site reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Interaction with tests
The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Streptococcal Infections
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account.

Hypoglycemia
As with other quinolones, hypoglycemiahas been reportedmost oftenin diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended.

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 risk of serious adverse reactions (including articular damage) in infants nursing from motherstaking 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
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine,olanzapine 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 (e.g. of theophylline) may be necessary.

Drugs known to prolong QT interval
Ciprofloxacin 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).

Probenecid
Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

Theophylline
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.

Other xanthine derivatives
On concurrentadministration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin
Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Cyclosporin
A transient risein the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin were 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 co-administration 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 ropinirde with ciprofloxacin, results in an increaseof Cmax and AUC of ropinirole. Monitoring of ropinirole-related side effects and dose adjustment, as appropriate, is recommended during and shortlyafter co-administration with ciprofoxacin.

Clozapine
Concomitantadministration of ciprofloxacin with dozapine increasesserum concentrations of clozapine andN-desmethylclozapine. Clinical surveillance andappropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil
Concomitant administration of ciprofloxacin with sildenafil increase Cmax and AUC of sildenafil. Therefore, caution should be used during prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Glyburide
The concomitant administration of ciprofloxacin with the sulfonylurea glyburide has resulted in severe hypoglycemia.

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.

OVERDOSAGE
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and hematuria. Reversible renal toxicity has been reported. Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.
Only a small quantity of ciprofloxacin (<10%) is eliminated by hemodialysis or peritoneal dialysis.
In the event of overdose,symptomatic treatmentshould be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

STORAGE
Store at 25°C (Excursions permitted between 15°C to 30°C).
Protect from light and heat.
Do not refrigerate or freeze.
Infusion vial should be removed from the box only immediately before use.

HOW SUPPLIED
Cipesta IV (Ciprofloxacin) Infusion 200mg/100mL is available in 1 vial.
Cipesta DS IV (Ciprofloxacin) Infusion 400mg/100mL is available in 1 vial.

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

L01-200007594