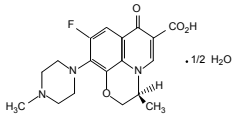
Leflox™

[Levofloxacin Tablets]

250mg, 500mg, 750mg

Tablets

LEFLOX (Levofloxacin) is a synthetic broad-spectrum antibacterial agent. Chemically, levofloxacin, a chiral fluorinated carboxyquinilone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin with a chemical name of: (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate.
The molecular formula is $C_{18}H_{20}FN_3O_{4\text{-}1/2}H_2O$ and the structural formula is:



Levofloxacin Hemihydrate

QUALITATIVE AND QUANTITATIVE COMPOSITION
LEFLOX (Levofloxacin) is available for oral administration as film-coated tablets:

1. LEFLOX (Levofloxacin) Tablet 250mg
   Each film-coated tablet contains:
   Levofloxacin…250mg

2. LEFLOX (Levofloxacin) Tablet 500mg
   Each film-coated tablet contains:
   Levofloxacin…500mg

3. LEFLOX (Levofloxacin) Tablet 750mg
   Each film-coated tablet contains:
   Levofloxacin…750mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The main mechanism of action of levofloxacin involves the inhibition of bacterial topoisomerase IV and DNA gyrase (both or which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination. Levofloxacin has *in vitro* activity against the following gram-negative and gram-positive micro-organisms. It is often bactericidal at concentrations equal to or slightly greater than inhibitory concentration. It is generally considered to be about twice as active as its isomer, ofloxacin.

Microbiology
Levofloxacin has been shown to be active against most strains of the following micro-organisms both *in vitro* and in clinical infections.

Commonly susceptible species
Aerobic Gram-positive bacteria
Staphylococcus aureus methicillin-susceptible, *Staphylococcus saprophyticus, Streptococci, group C and G, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes.*

Aerobic Gram- negative bacteria
Burkholderia cepacia, Eikenella corrodens, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella oxytoca, Klebsiella pneumoniae, Moraxella catarrhalis, Pasteurella multocida, Proteus vulgaris, Providencia rettgeri.

Anaerobic bacteria
Peptostreptococcus

Other
Chlamydophila pneumoniae, Chlamydophila *psittaci, Chlamydia trachomatis, Legionella pneumophila, Mycoplasma pneu moniae, Mycoplasma hominis, Ureaplasma urealyticum.*

Species for which acquired resistance may be a problem
Aerobic Gram-positive bacteria
Enterococcus faecalis, Staphylococcus aureus methicillin-resistant, Coagulase negative *Staphylococcus spp.*

Aerobic Gram- negative bacteria
Acinetobacter baumannii, Citrobacter freundii, Enterobacter aerogenes, Enterobacter agglomerans, Enterobacter cloacae, Escherichia coli, Morganella morganii, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Serratia marcescens.

Anaerobic bacteria
Bacteroides fragilis, Bacteroides ovatus, Bacteroides thetaiotam icron, Bacteroides vulgatus, Clostridium difficile.

Levofloxacin has been shown to be active against *Bacillus anthracis in vitro.*

Pharmacokinetics
Levofloxacin is rapidly and almost completely absorbed with absolute bioavailability of 99% following oral use with peak plasma concentrations achieved within 1-2 hours of a dose. The mean volume of distribution of Levofloxacin ranges from 74 to 112 L after single or multiple 500mg or 750mg doses indicating distribution into body tissues including the bronchial mucosa and lungs, but penetration into CSF is relatively poor. Levofloxacin is approximately 24 to 38% bound to plasma proteins. It is only metabolised to a small degree to in-active metabolites. The elimination half-life of Levofloxacin is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours and less than 5% of an administered dose is recovered in the urine. It is not removed by hemodialysis or peritoneal dialysis.

Special Population
Renal Insufficiency
Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal func tion (creatinine clearance <50mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD.

THERAPEUTIC INDICATIONS
LEFLOX (Levofloxacin) tablets are indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated micro-organisms in the conditions listed below:

- Acute bacterial sinusitis.
- Acute bacterial exacerbation of chronic bronchitis.
- Community-acquired pneumonia and nosocomial pneumonia.
- Complicated skin and skin structure infections.
- Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections.
- Chronic bacterial prostatitis.
- Complicated urinary tract infections (mild to moderate).
- Uncomplicated urinary tract infections (mild to moderate).
- Acute pyelonephritis (mild to moderate).
- Inhalational anthrax, post-exposure.

DOSAGE AND ADMINISTRATION
LEFLOX (Levofloxacin) tablets 250mg, 500mg and 750mg administered orally every 24 hours. The dosage depends on the types and severity of the infections and the sensitivity of the presumed, causative pathogen.
LEFLOX (Levofloxacin) should be swallowed without crushing and with sufficient amount of liquid. LEFLOX (Levofloxacin) tablets can be administered without regard to food. LEFLOX (Levofloxacin) tablets should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets or the pediatric powder for oral solution. The dosage guidelines as per the infection are given as under:

Dosage in adult patients with normal renal function (creatinine clearance ≥ 50mL/min)

INDICATIONS	DAILY DOSE (mg)	DURATION (DAYS)
Acute Bacterial Sinusitis	500mg od	10 - 14
	750mg	5
Acute Bacterial Exacerbation of chronic Bronchitis	250mg to 500mg once daily	7 - 10
Community Acquired Pneumonia	500mg od or bid	7 - 14
	750mg od	5
Nosocomial Pneumonia	750mg od	7 - 14
Uncomplicated skin and skin soft tissue Infections	500mg od	7 - 10
Complicated skin and soft tissue Infections	750mg od	7 - 14
Uncomplicated Urinary Tract Infections	250mg od	3
Complicated Urinary Tract Infections	250mg od	10
	750mg od	5
Acute Pyelonephritis	250mg od	10
	750mg od	5
Chronic Bacterial Prostatitis	500mg od	28
Inhalational Anthrax (Post-Exposure)	500mg	60

Dosage in adult patients with impaired renal function (creatinine clearance < 50mL/min)

Dosage in Normal Renal Functions Every 24 hours	Creatinine Clearance 20 to 49mL/min	Creatinine Clearance 10 to 19mL/min	Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)
750mg	750mg every 48 hours	750mg initial dose, then 500mg every 48 hours	750mg initial dose, then 500mg every 48 hours
500mg	500mg initial dose, then 250mg every 24 hours	500mg initial dose, then 250mg every 48 hours	500mg initial dose, then 250mg every 48 hours
250mg	No dosage adjustment	250mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment is required	No information on dosing adjustment is available

ADVERSE REACTIONS
Levofloxacin is usually well tolerated. However, following are the adverse effects reported during its therapy.

Common: Moniliasis, insomnia, headache, dizziness, dyspnea, nausea, diarrhea, constipation, abdominal pain, vomiting, dyspepsia, rash, pruritus, vaginitis, edema, chest pain.

Less common: Genital moniliasis, anemia, thrombocytopenia, granulocytopenia, allergic reaction, hyperglycemia, hypoglycemia, hyperkalemia, anxiety, agitation, confusion, depression, hallucination, nightmare, sleep disorder, anorexia, abnormal dreaming, tremor, convulsions, paresthesia, vertigo, hypertonia, hyperkinesias, abnormal gait, somnolence, syncope, epistaxis, cardiac arrest, palpitation, ventricular tachycardia, ventricular arrhythmia, phlebitis, gastritis, stomatitis, pancreatitis, esophagitis, gastroenteritis, glossitis, pseudomembraneous/*C. difficile* colitis, abnormal hepatic function, increased hepatic enzymes, increased alkaline phosphatase, urticaria, arthralgia, tendonitis, myalgia, skeletal pain, abnormal renal function, acute renal failure.

CONTRAINDICATIONS
Levofloxacin is contraindicated in

- Patients with a history of hypersensitivity to this drug and/or other quinolone antibacterial.
- Children or growing adolescents.

WARNIING

Fluoroquinolones, including Levofloxacin 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.
Fluoroquinolones, including Levofloxacin may exacerbate muscle weakness in persons with myasthenia gravis. Avoid in patients with known history of myasthenia gravis.

- Serious adverse events requiring ventilatory support have been associated with fluoroquinolone use, in persons with myasthenia gravis.

PRECAUTIONS
General
Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of highly concentrated urine.

Tendinitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis.

Clostridium difficile-associated disease
Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin may be symptomatic of *Clostridium difficile*-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, levofloxacin must be stopped immediately and patients should be treated with supportive measures with specific therapy without delay.

Patients predisposed to seizures
Quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline.

Patients with G-6- phosphate dehydrogenase deficiency
Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution.

Hypoglycemia
As with all quinolones, hypoglycemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitisation
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomittantly.

Psychotic reactions
Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

QT interval prolongation
Caution should be taken when using fluoroquinolones, including levofloxacin, 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)
- elderly
- cardiac disease (e.g., heart failure, myocardial infarction, bradycardia)

Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Opiates
In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Hepatobiliary disorders
Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Renal Insufficiency
Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD.

Geriatric Use
Caution should be used when prescribing Levofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of these potential side effects and advised to discontinue levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

Pregnancy
There are no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Because of the potential for serious adverse reactions from levofloxacin in nursing 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
Antacids, Sucralfate, Metal Cations, Multivitamins: Concurrent administration of levofloxacin with antacids containing magnesium, or aluminium, as well as sucralfate metal cations such as iron and multivitamin preparations with zinc or didanosine may interfere with the gastrointestinal absorption of levofloxacin resulting in systemic levels considerably lower than desired. These agents should be taken at least 2 hours before or 2 hours after levofloxacin administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs: Pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.
Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and Cimetidine: Caution should be exercised when levofloxacin is co-administered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Cyclosporine: The half-life of ciclosporine was increased by 33% when co-administered with levofloxacin.

Warfarin: There have been reports in patients that levofloxacin enhances the effects of warfarin. Prothrombin time, International Normalized Ratio (INR) or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

OVERDOSAGE
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

HOW SUPPLIED
LEFLOX Tablets 250mg are available in blister pack of 10's.
LEFLOX Tablets 500mg are available in blister pack of 10's.
LEFLOX Tablets 750mg are available in blister pack of 10's.

STORAGE
Store below 30°C.
Protect from sunlight & moisture.
The expiration date refers to the product correctly stored at the required conditions.

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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EX09-200007596

Manufactured by: Getz Pharma (Pvt.) Limited, 29-30/27, K.I.A., Karachi - 74900, Pakistan.