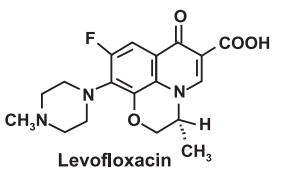
Leflox™

[Levofloxacin USP]

500mg/100mL
750mg/150mL
I.V. Infusion

DESCRIPTION

LEFLOX (Levofloxacin) is a synthetic broad-spectrum antibacterial agent. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, 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-piperazinyl)-7-oxo-7H pyrido [1,2,3,-de] [1,4] benzoxazine-6-carboxylic acid.
The molecular formula is $C_{18}H_{20}FN_3O_4$ and the structural formula is:



Levofloxacin

QUALITATIVE AND QUANTITATIVE COMPOSITION

LEFLOX (Levofloxacin) Infusion is available as:

1. LEFLOX I.V Infusion 500mg/100mL
   Each mL solution for infusion contains:
   Levofloxacin USP...5mg

2. LEFLOX I.V Infusion 750mg/150mL
   Each mL solution for infusion contains:
   Levofloxacin USP...5mg

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 topoisomearse), 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.

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 para-influenzae.
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 pneumoniae.
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 thetaiotamicron.
Bacteroides vulgatus.
Clostridium difficile.

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

Pharmacokinetics

Absorption
Following a single intravenous dose of levofloxacin, the mean ±SD peak plasma concentration attained was 6.2 ±1.0µg/mL after a 500mg dose infused over 60 minutes and 11.5 ±4.0µg/mL after a 750mg dose infused over 90 minutes.
Levofloxacin IV pharmacokinetics are linear and predictable after single and multiple dosing regimens. Steady state conditions are reached within 48 hours following a 500mg or 750mg once daily dosage regimens. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily I.V. regimens were approximately 6.4 ±0.8 and 0.6 ±0.2µg/mL after the 500mg doses 12.1 ± 4.1 and 1.3 ±0.71•g/mL after the 750mg doses, respectively.

Distribution
The mean volume of distribution generally ranges from 74 – 112 litres after single and multiple dosing of 500mg or 750mg dose, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in body fluid of healthy subjects at approximately 3 hours after dosing.

Levofloxacin is approximately 24 to 38% bound to serum proteins. Levofloxacin is mainly bound to serum albumin in humans. The binding of levofloxacin to serum proteins is independent of the drug concentration.

Metabolism and Elimination
Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. The mean terminal elimination half-life ($t^1/_2$) of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin. The mean apparent total body clearance and renal clearance range from approx. 144-226mL/min and 96-142mL/min respectively.

Special Population
Pediatric Patients
The pharmacokinetics of levofloxacin follwoing a single 7mg/kg intravenous dose in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposure than adults for a given mg/kg dose, dosage regimen of 8 mg/kg every 12 hours (not to exceed 250mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures ($AUC_{0\text{-}24}$ and C_{max}) to those observed in adult patients administered 500mg of levofloxacin once every 24 hours.

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.

Hepatic insufficiency
Pharmacokinetic studies in hepatically impaired patients have not been conducted.
Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

THERAPEUTIC INDICATIONS

LEFLOX (Levofloxacin) I.V. Infusion is indicated for the treatment of adults with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below.
- Nosocomial pneumonia
- Community acquired pneumonia
- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Uncomplicated skin and soft tissue infections.
- Complicated skin and soft tissue infections
- Chronic bacterial prostatitis
- Complicated urinary tract infections
- Uncomplicated urinary tract infections
- Acute pyelonephritis
- Inhalation anthrax (post-exposure)

DOSAGE AND ADMINISTRATION

LEFLOX (Levofloxacin) I.V. Infusion is indicated when intravenous administration offers a route of administration advantageous to the patient. Rapid or bolus intravenous infusion must be avoided. The usual dose of LEFLOX (Levofloxacin) I.V. Infusion is 250mg or 500mg administered by slow infusion over 60 minutes every 24 hours or 750mg administered by slow infusion over 90 minutes every 24 hours. The dosage depends on the types and severity of the infections and the sensitivity of the presumed causative pathogen. LEFLOX (Levofloxacin) I.V. Infusion should not be mixed with heparin or alkaline solutions (e.g., sodium hydrogen carbonate).

The dosage guidelines as per the infection are given as under.

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

INDICATIONS	Dose every 24 hours	DURATION (DAYS)
Acute bacterial sinusitis	500mg	10 – 14
	750mg	5
Acute bacterial exacerbation of chronic Bronchitis	500mg	7
Community Acquired pneumonia	500mg	7 – 14
	750mg	5
Nosocomial pneumonia	750mg	7 – 14
Uncomplicated skin and soft tissue infections	500mg	7-10
Complicated skin and soft tissue infections	750mg	7 – 14
Uncomplicated urinary tract infections	250mg	3
Complicated urinary tract infections	750mg	5
	250mg	10
Acute pyelonephritis	750mg	5
	250mg	10
Chronic bacterial prostatitis	500mg	28
Inhalation anthrax (post-exposure)*		
Adults	500mg	60
Pediatric patients >50Kg and >6 months of age	500mg once every 24h	60
Pediatric patients <50Kg and >6 months of age	8mg/Kg (not to exceed 250mg per dose) once every 12h	60

*Note:Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B.anthracis*.

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

Dosage in Normal Renal Function Every 24 hrs	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 required	250mg every 48 hours. If treating uncomplicated UTI then no dosage adjustment 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 injection site reaction, 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, tendinitis, myalgia, skeletal pain, abnormal renal function, acute renal failure.

CONTRAINDICATIONS
Levofloxacin is contraindicated in patients:
- with a known hypersensitivity to this drug and/or other fluoroquinolone antibacterials.
- with epilepsy
- with history of tendon disorders related to fluoroquilone administration

WARNING

Floroquinolones, 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.

PRECAUTIONS
General
No fluoroquinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous.

Infusion Time
The recommended infusion time of at least 30 minutes for 250mg, 60 minutes for 500mg or 90 minutes for 750mg lefloxacin solution for infusion should be observed. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, the infusion must be halted immediately.

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 solution for infusion, may be symptomatic of *Clostridium difficile* associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, levofloxacin solution for infusion 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 hemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution.

Patients with renal impairment
Since Levofloxacin is excreted mainly by the kidneys, the dose of Levofloxacin should be adjusted in patients with renal impairment.

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 concomitantly.

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).
- 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
Levofloxacin should be administered with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearence<50mL/min), adjustment of dose regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearence.

Pregnancy
The safety and efficacy of levofloxacin in pregnant women has not been established. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, nursing should not be undertaken by mothers who must use levofloxacin.

Drug interactions
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 coadministered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Cyclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

HOW SUPPLIED
LEFLOX (Levofloxacin) I.V. 500mg is available in 1x100mL vial.
LEFLOX (Levofloxacin) I.V. 750mg is available in 1x150mL vial.

STORAGE
Store below 25°C.
Do not refrigerate.
Protect from sunlight.
Once the vial is removed from the carton the infusion solution must be used within three days.
Once the vial has been opened, the infusion solution must be used within three hours.

The expiration date refers to the product correctly stored at the required conditions.
Keep in the pack until required.

Keep out of the 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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