

Levofloxacin (as Hemihydrate)

Levocin

5mg/mL Solution for I.V. Infusion

Antibacterial

DESCRIPTION

Levofloxacin (Levocin) 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 $C_{18}H_{20}FN_4O_3$, and the structural formula is:



FORMULATION

Levofloxacin (Levocin) IV is available as:

Levofloxacin (Levocin) IV Infusion 500mg/100mL

Each mL solution for infusion contains:

Levofloxacin ... 5mg (as Hemihydrate)

Levofloxacin (Levocin) IV Infusion 750mg/150mL

Each mL solution for infusion contains:

Levofloxacin ... 5mg (as Hemihydrate)

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 of 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 microorganisms. 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.
Erkennia corrodens.
Haemophilus influenzae.
Haemophilus para-influenzae.
Klebsiella oxytoca.
Klebsiella pneumoniae.
Moraxella catarrhalis.
Pasteurella multocida.
Proteus vulgaris.
Providencia rettgeri.

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydia pneumoniae
Chlamydia 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 \pm SD peak plasma concentration attained was 6.2 \pm 1.0 μ g/mL after a 500mg dose infused over 60 minutes and 11.5 \pm 4.0 μ g/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 \pm SD peak and trough plasma concentrations attained following multiple once-daily I.V. regimens were approximately 6.4 \pm 0.8 and 0.6 \pm 0.2 μ g/mL after the 500mg doses 12.1 \pm 4.1 and 1.3 \pm 0.71 μ 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 following 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 0-24 and C_{min}) 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

Levofloxacin (Levocin) 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

Levofloxacin (Levocin) 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 Levofloxacin (Levocin) 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. Levofloxacin (Levocin) 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
	500mg	7 – 14
Community Acquired pneumonia	750mg	5
	750mg	7 – 14
Nosocomial pneumonia	750mg	7 – 14
	500mg	7-10
Uncomplicated skin and soft tissue infections	750mg	7 – 14
	250mg	3
Uncomplicated urinary tract infections	750mg	5
	250mg	10
Complicated urinary tract infections	750mg	5
	250mg	10
Chronic bacterial prostatitis	500mg	28
	500mg	60
Inhalation anthrax (post-exposure)*	500mg	60
	500mg once every 24h	60
Pediatric patients >50Kg and \geq 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 \leq 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, pseudomembranous colitis, clostridium difficile, 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 known hypersensitivity to this drug and/or other fluoroquinolone antibacterials.
- with epilepsy.
- with history of tendon disorders related to fluoroquinolone administration.

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 Levofloxacin 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 fenflurine 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 photosensitization

Although photosensitization 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 photosensitization.

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 clearance $<$ 50mL/min), adjustment of dose regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance.

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

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent (e.g., glyburide/glibenclamide) or insulin. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

Multivalent cations: No quinolone should be co-administered with any solution containing multivalent cations, e.g. magnesium, through the same intravenous line.

Overdosage

Levofloxacin exhibits a low potential for acute toxicity. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

AVAILABILITY

Levofloxacin (Levocin) I.V. 500mg/100mL is available in 1x100 mL vial.
Levofloxacin (Levocin) I.V. 750mg/150mL is available in 1x150 mL vial.

STORAGE

Store at temperatures not exceeding 30°C.
Do not refrigerate.
Protect from light.
Keep in the pack until required.
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 out of reach of children.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription. For suspected adverse drug reaction, report to FDA: www.fda.gov/ph

REGISTRATION NUMBER

Levocin Solution for IV Infusion 500mg/100ml: DR-XY37693
Levocin Solution for IV Infusion 750mg/150mL: DR-XY41146

DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Levocin Solution for IV Infusion 500mg/100ml
Initial: 29 March, 2010
Renewal: 26 June, 2015
Revalidated: 19 July, 2017

Levocin Solution for IV Infusion 750mg/150mL
Initial: 14 August, 2012

DATE OF REVISION OF PACKAGING INSERT 6 October, 2017.

**Please read the contents carefully before use.
This package insert is continually updated from time to time.**



PH-200009759

Manufactured by: Getz Pharma (Pvt.) Ltd., 29-30/27, K.I.A., Karachi - 74900, Pakistan.
Imported by: Getz Pharma (Phils.) Inc., 2/F Tower 1, The Rockwell Business Center, Ortigas Ave., Pasig City, Philippines.