Summary of Product Characteristics for Pharmaceutical Products

1. NAME OF DRUG PRODUCT

Leflox 500mg/100mL Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution for infusion contains:
Levofloxacin USP . . . 5mg

3. PHARMACEUTICAL FORM

Light yellow clear liquid filled in clear glass vial with blue color flip off seal having FLIP OFF embossed on top and grey rubber stopper.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LEFLOX I.V. Infusion is indicated for the treatment of adults (≥18 years of age) 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 skin structure infections.
- Complicated skin and skin structure infections
- Chronic bacterial prostatitis
- Complicated urinary tract infections
- Uncomplicated urinary tract infections
- Acute pyelonephritis
- Inhalation anthrax (post-exposure)

4.2 Posology and method of administration

LEFLOX I.V. Infusion should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Rapid or Bolus Intravenous Infusion Must Be Avoided. LEFLOX I.V. Infusion should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage.

The usual dose of LEFLOX Tablets is 500mg or 750mg administered orally every 24 hours, as indicated by infection. The usual dose of LEFLOX I.V. Infusion is 500mg administered by slow infusion over 60 minutes every 24 hours or 750mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection.

LEFLOX Tablets can be administered without regard to food.
Oral doses 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 Videx (didanosine), chewable/buffered tablets or the pediatric powder for oral solution.
The dosage guidelines as per the infection are given as under.

Dosage in Patients with Normal Renal Function

Infection[1]	Unit Dose	Freq.	Duration[2]	Daily Dose
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Comm. Acquired Pneumonia	750 mg[3]	q24h	5 days	750 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Sinusitis	500 mg	q24h	10-14 days	500 mg
Acute Bacterial Sinusitis	750 mg	q24h	5 days	750 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg
Inhalational anthrax (post-exposure) Adult [4, 5]	500 mg	q24h	60 days[5]	500mg

Dosage in Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis/Comm. Acquired Pneumonia/Acute Bacterial Sinusitis/Uncomplicated SSSI/Chronic Bacterial Prostatitis/Inhalational Anthrax (post-exposure)		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI/Nosocomial Pneumonia/ Comm. Acquired Pneumonia/Acute Bacterial Sinusitis		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI/Acute Pyelonephritis		
$CL_{CR} \geq 20$ mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR}=creatinine clearances
CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance:

Mean: Creatinine Clearance (mL/min) = $\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/dL)}}$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

4.3 Contraindications

Leflox is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

4.4 Special warnings and special precautions for use

General

Prescribing Levofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Because a rapid or bolus intravenous injection may result in hypotension, levofloxacin injection should only be administered by slow intravenous infusion over a period of 60 or 90 minutes depending on the dosage.

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

Administer Levofloxacin 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 the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance.

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction).

As with other quinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide/glibenclamide) or with insulin.

In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately.

Torsades de pointes

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving quinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients

receiving class IA (quinidine, procainamide), or class III (amiodarone, sotalol) antiarrhythmic agents.
As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy.

Tendon Effects
Ruptures of the shoulder, hand, Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

Hypersensitivity
Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions.
Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Peripheral Neuropathy
Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Pseudomembranous colitis
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis."

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against C. difficile colitis.

Information for Patients

Patients should be advised:

- Patients should be counseled that antibacterial drugs including LEFLOX (levofloxacin) should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LEFLOX is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may decrease the effectiveness of the immediate treatment and increase the likelihood that bacteria will develop resistance and will not be treatable by LEFLOX or other antibacterial drugs in the future;
- that peripheral neuropathies have been associated with levofloxacin use. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, they should discontinue treatment and contact their physicians.
- to drink fluids liberally;
- that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx (didanosine) should be taken at least two hours before or two hours after oral levofloxacin administration.
- that levofloxacin oral tablets can be taken without regard to meals
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination;
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs.
- that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician.
- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin.
- that convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

4.5 Interaction with other medicaments

Antacids, Sucralfate, Metal Cations, Multivitamins

Levofloxacin Tablets

While the chelation by divalent cations is less marked than with other quinolones, concurrent administration of Levofloxacin Tablets with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or Videx (didanosine) may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired.

These agents should be taken at least two hours before or two hours after levofloxacin administration.

Levofloxacin Injection

There are no data concerning an interaction of intravenous quinolones with oral antacids sucralfate, multivitamins, Videx (didanosine), or metal cations. However, no quinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line.

Theophylline

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels.

Warfarin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. There have been reports during the post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. 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.

Cyclosporine

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and t½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin.

Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

Probenecid and Cimetidine:

No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and t½ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and CLR were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is 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.

Antidiabetic agents:

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

4.6 Pregnancy and Lactation

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.

Lactation

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, 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.

4.7 Effects on ability to drive and use machine

Levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination.

4.8 Undesirable effects

Body as a Whole – General Disorders:

Ascites, allergic reaction, asthenia, edema, fever, headache, hot flashes, influenza-like symptoms, leg pain, malaise, rigors, substernal chest pain, syncope, multiple organ failure, changed temperature sensation, withdrawal syndrome.

Cardiovascular Disorders, General:

Cardiac failure, hypertension, hypertension aggravated, hypotension, postural hypotension.

Central and Peripheral Nervous System Disorders:

Convulsions (seizures), hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contractions, migraine, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo, encephalopathy, abnormal gait, leg cramps, intracranial hypertension, ataxia.

Gastro-Intestinal System Disorders:

Dry mouth, dysphagia, esophagitis, gastritis, gastroesophageal reflux, G.I. hemorrhage, glossitis, intestinal obstruction, pancreatitis, tongue edema, melena, stomatitis.

Hearing and Vestibular Disorders:

Earache, ear disorder NOS, tinnitus.

Heart Rate and Rhythm Disorders:

Arrhythmia, arrhythmia ventricular, atrial fibrillation, bradycardia, cardiac arrest, ventricular fibrillation, heart block, palpitation, supraventricular tachycardia, ventricular tachycardia, tachycardia.

Liver and Biliary System Disorders:

Abnormal hepatic function, cholecystitis, cholelithiasis, hepatic enzymes increased, hepatic failure, jaundice.

Metabolic and Nutritional Disorders:

Hypomagnesemia, thirst, dehydration, electrolyte abnormality, fluid overload, gout, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hyponatremia, hypophosphatemia, nonprotein nitrogen increase, weight decrease.

Musculo-Skeletal System Disorders:

Arthralgia, arthritis, arthrosis, myalgia, osteomyelitis, skeletal pain, synovitis, tendonitis, tendon disorder.

Myo, Endo, Pericardial and Valve Disorders:
Angina pectoris, myocardial infarction.

Neoplasms:
Carcinoma, thrombocythemia.

Other Special Senses Disorders:
Parosmia, taste perversion.

Platelet, Bleeding and Clotting Disorders:
Hematoma, epistaxis, prothrombin decreased, pulmonary embolism, purpura, thrombocytopenia.

Psychiatric Disorders:
Abnormal dreaming, agitation, anorexia, anxiety, confusion, depression, hallucination, impotence, nervousness, paroniria, sleep disorder, somnolence.

Red Blood Cell Disorders:
Anemia.
Reproductive Disorders:
Dysmenorrhea, leucorrhea.

Resistance Mechanism Disorders:
Abscess, bacterial infection, fungal infection, herpes simplex, moniliasis, otitis media, sepsis, infection.

Respiratory System Disorders:
Airways obstruction, aspiration, asthma, bronchitis, bronchospasm, chronic obstructive airway disease, coughing, hemoptysis, epistaxis, hypoxia, laryngitis, pleural effusion, pleurisy, pneumonitis, pneumonia, pneumothorax, pulmonary edema, respiratory depression, respiratory disorder, respiratory insufficiency, upper respiratory tract infection.

Skin and Appendages Disorders:
Alopecia, bullous eruption, dry skin, eczema, genital pruritus, increased sweating, rash, skin disorder, skin exfoliation, skin ulceration, urticaria.

Urinary System Disorders:
Abnormal renal function, acute renal failure, hematuria, oliguria, urinary incontinence, urinary retention, urinary tract infection.

Vascular (Extracardiac) Disorders:
Flushing, cerebrovascular disorder, gangrene, phlebitis, purpura, thrombophlebitis (deep).

Vision Disorders:
Abnormal vision, eye pain, conjunctivitis.

White Cell and RES Disorders:
Agranulocytosis, granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal NOS.

Post-Marketing Adverse Reactions
Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis, anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio (INR)/prothrombin time, peripheral neuropathy, rhabdomyolysis, Stevens-Johnson Syndrome, tendon rupture, torsades de pointes, vasodilation.

'Reporting of suspected adverse reactions: Healthcare professionals are requested to report any Suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org'

4.9 OVERDOSE

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500mg/kg orally and 250mg/kg I.V. produced significant mortality in rodents.
In the event of an acute overdosage, the stomach should be emptied. The is not efficiently removed by hemodialysis or peritoneal dialysis.

5.PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:

Fluoroquinolones

ATC-code: J01MA12

Mechanism of action
Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves 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.
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.*

5.2 Pharmacokinetic properties

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500mg tablet and a 750mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 µg/mL after a 500mg dose infused over 60 minutes and 11.5 ±4.0 µg/mL after a 750mg dose infused over 90 minutes.

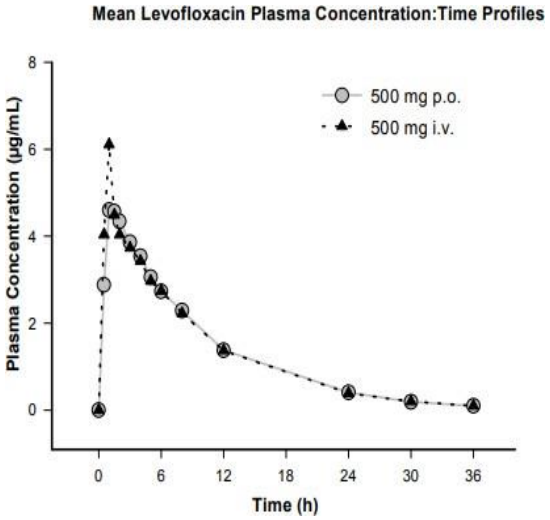
Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or I.V. dosing regimens. Steady-state conditions are reached within 48 hours following a 500mg or 750mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2µg/mL after the 500mg doses, and 8.6 ±1.9 and 1.1 ±0.4µg/mL after the 750mg doses, respectively. The mean ±SD peak and trough plasma

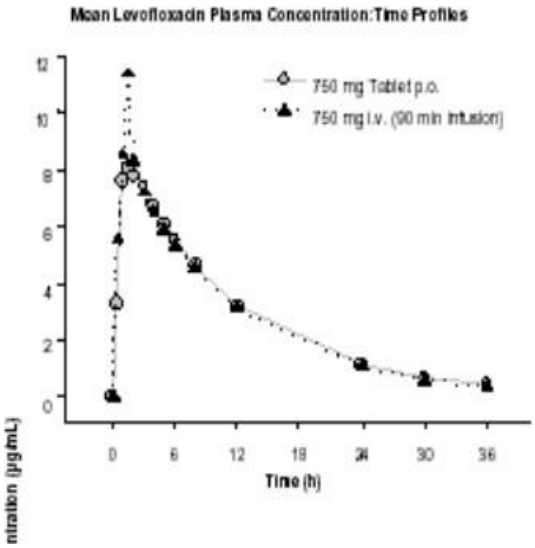
concentrations attained following multiple once-daily i.v. regimens were approximately 6.4 ±0.8 and 0.6 ±0.2µg/mL after the

500mg doses, and 12.1 ±4.1 and 1.3 ±0.71µg/mL after the 750mg doses, respectively.

Oral administration of 500mg Levofloxacin Tablet with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, Levofloxacin tablets can be administered without regard to food.

The plasma concentration profile of levofloxacin after I.V administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and I.V routes of administration can be considered interchangeable.





Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500mg or 750mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750mg and 500mg levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5- fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 µg/g over a 24-hour period after a single 500mg oral dose. In vitro, over a clinically relevant range (1 to 10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method.

Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, 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. 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. These metabolites have little relevant pharmacological activity.

Elimination

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of

levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Special population

Geriatric:

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500mg oral dose of levofloxacin to healthy elderly subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.

Pediatric:

The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender:

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal

function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race:
The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from white and non-whites subjects. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

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.

Bacterial infection:
The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100mg/kg/day) was 1.4 times the highest recommended human dose (750mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh- 1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from
25 to 42μg/g at the highest levofloxacin dose level (300mg/kg/day) used in the photo- carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750mg of levofloxacin averaged approximately 11.8μg/g at C_{max}.
Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line)

and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

6.PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid
Sodium Hydroxide
Water for injection

6.2 Incompatibilities

None

6.3 Shelf-life

3 Years

The expiration dates refer to the product correctly stored in the required conditions.

6.4 Special precautions for storage

- Store below 25℃.
- Do not refrigerate.
- Keep in the pack until required.
- 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.
- *Keep out of reach of children.*

6.5 Nature and contents of container

Leflox IV Infusion 500mg/100mL are available in Clear glass USP type II 100mL vial of 1's (1 x 100mL Vial) packed in printed carton along with the package insert.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- To be sold on prescription of a registered medical practitioner only.
- Once the vial is removed from the carton the infusion solution must be used within three days.
- Keep out of the reach of children.

7.MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER

16830; H2005/465

9.DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

1st November, 2005

10. DATE OF REVISION OF THE TEXT

20th February, 2026