• LEVOX 750 mg/150 mL Intravenous Infusion Package Insert (Front) V. 2

UNILAB

Levofloxacin hydrate

Levox®

750 mg/150 mL Solution for Intravenous Infusion
ANTIBACTERIAL (Fluoroquinolone)

Rx

FORMULATION
Each 150 mL solution for infusion contains:
Levofloxacin (as hydrate)..... 750 mg

PRODUCT DESCRIPTION
A clear greenish-yellow solution for infusion in a transparent vial.

CLINICAL PHARMACOLOGY

PHARMACODYNAMICS
Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antibacterial agent. The mechanism of action of levofloxacin and other quinolones involves inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV enzymes which are essential for DNA replication, transcription, repair, and recombination.

ANTIMICROBIAL SPECTRUM OF ACTIVITY
Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections:

Aerobic Gram-positive	Aerobic Gram-negative
Enterococcus faecalis *Staphylococcus aureus* (methicillin-susceptible strains) *Staphylococcus epidermidis* (methicillin-susceptible strains) *Staphylococcus saprophyticus* *Streptococcus pneumoniae*, including multi-drug resistant strains (MDRSP) *Streptococcus pyogenes*	*Enterobacter cloacae* *Escherichia coli* *Haemophilus influenzae* *Haemophilus parainfluenzae* *Klebsiella pneumoniae* *Legionella pneumophila* *Moraxella catarrhalis* *Proteus mirabilis* *Pseudomonas aeruginosa** *Serratia marcescens*
Other Microorganisms	
Chlamydophila pneumoniae	*Mycoplasma pneumoniae*

*As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Levofloxacin has been shown to be active *in vitro* against most strains of the following organisms; however, the clinical significance of these data is unknown:

Aerobic Gram-positive	Aerobic Gram-negative	
Staphylococcus haemolyticus *Streptococcus* **(Group C/F)** *Streptococcus* **(Group G)** *Streptococcus agalactiae* *Streptococcus milleri* *Viridans group streptococci* *Bacillus anthracis**	*Acinetobacter baumannii* *Acinetobacter lwoffii* *Bordetella pertussis* *Citrobacter koseri* *Citrobacter freundii* *Enterobacter aerogenes* *Enterobacter sakazakii*	*Klebsiella oxytoca* *Morganella morganii* *Pantoea agglomerans* *Proteus vulgaris* *Providencia rettgeri* *Providencia stuartii* *Pseudomonas fluorescens* *Yersinia pestis*
Anaerobes		
Clostridium perfringens		

*Levofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of plasma levels as a surrogate marker in a rhesus monkey model for anthrax (post-exposure).

It is suggested to carry out susceptibility tests.

PHARMACOKINETICS

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral/intravenous (IV) dosing regimens. Steady-state conditions are reached within 48 hours after a 500 mg or 750 mg once daily dosage regimen. The oral and IV route of administration may also be considered interchangeable since levofloxacin's plasma concentration profiles are nearly superimposable in the post-peak, distribution-elimination phase.

The mean volume of distribution generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Penetration of levofloxacin in skin tissues and in blister fluid is rapid and extensive. It also penetrates well into lung tissues. Protein binding is approximately 24% to 38% and is independent of drug concentration.

Levofloxacin is stereochemically stable in plasma and urine and undergoes limited metabolism in humans with less than 5% of an administered dose recovered in the urine.

Plasma half-life ($t_{1/2}$) ranges from approximately 6 to 8 hours. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/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.

INDICATIONS

For the treatment of adults (≥ 18 years old) with mild, moderate, or severe infections caused by susceptible strains of the designated microorganisms for the following conditions:

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

To reduce the incidence or progression of inhalational anthrax in adults and children ≥ 6 months old, following exposure to aerosolized *Bacillus anthracis*. The effectiveness of levofloxacin is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax.

For the treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* and prophylaxis for plague in adults and children ≥ 6 months old. Efficacy studies of levofloxacin could not be conducted in humans with plague for ethical and feasibility reasons. The approval of this indication was based on an efficacy study done in animals.

DOSAGE AND MODE OF ADMINISTRATION

Patients receiving oral or intravenous (IV) levofloxacin should be well hydrated to prevent formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones.

Levofloxacin should be given or taken at the same time each day.

Levofloxacin solution for infusion should only be administered by IV infusion. *It is **NOT** for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.*

Caution: Rapid or bolus IV infusion must be avoided because it may result to hypotension.

Usual Recommended Dose: 750 mg administered by slow IV infusion over 90 minutes once every 24 hours. The dose and duration of treatment are based on the type and severity of infection being treated (see **Dosing Table**).

As with other parenteral antibiotic therapy in general, administration of levofloxacin solution for infusion should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained. It is usually possible to switch from initial IV treatment to the oral route after a few days, depending on the patient's condition and the physician's discretion.

Levofloxacin IV Dosing in Adult Patients with Normal Renal Function (creatinine clearance ≥ 50 mL/min):

Infections	Once a Day Levofloxacin Oral or IV Dose	Duration of Treatment
Acute bacterial sinusitis	500 mg	10 to 14 days
	750 mg	5 days
Acute bacterial exacerbation of chronic bronchitis	500 mg	7 days
	750 mg	5 days
Community-acquired pneumonia	500 mg[1]	7 to 14 days
	750 mg[2]	5 days
Healthcare-associated pneumonia	750 mg	7 to 14 days
Complicated skin and skin structure infections (SSSI)	750 mg	7 to 14 days
Uncomplicated SSSI	500 mg	7 to 10 days
Complicated urinary tract infections (cUTI)	250 mg[3]	10 days
	750 mg[4]	5 days
Acute pyelonephritis (AP)	250 mg[3]	10 days
	750 mg[4]	5 days
Chronic bacterial prostatitis	500 mg	28 days
Uncomplicated urinary tract infections	250 mg	3 days
Inhalational anthrax (post-exposure)	500 mg[5]	60 days[6]
Plague	500 mg[7]	10 to 14 days

[1]Due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant strains), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae*

[2] Due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains), *Haemophilus influenzae, Haemophilus parainfluenzae, Chlamydophila pneumoniae,* or *Mycoplasma pneumoniae*

[3]This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*, and for AP due to E.coli.

[4]This regimen is indicated for cUTI due to *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and for AP due to *E. coli*, including cases with concurrent bacteremia.

[5]Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit.

[6]The safety of levofloxacin in adults for durations of therapy beyond 28 days has not been studied. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk.

[7]Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*. Higher doses of levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

Levofloxacin IV Dosing in Adult Patients with Renal Impairment (creatinine clearance < 50 mL/min):

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

When only the serum creatinine value is available, the following formula may be used to estimate creatinine clearance. The serum creatinine should represent a steady state of renal function:

Men: CLCR (mL/min) = $\frac{\text{Weight (kg) x (140 – age in years)}}{\text{72 x serum creatinine (mg/dL)}}$

Women: 0.85 x value calculated using the above formula

Levofloxacin Oral or IV Dosing in Children:

Infections	Levofloxacin Oral or IV Dose[1]	Duration of Treatment
Inhalational Anthrax (Post-Exposure)[2]		
Children ≥ 50 kg	500 mg once every 24 hours	60 days[3]
Children < 50 kg and ≥ 6 months old	8 mg/kg body weight per dose (not to exceed 250 mg per dose) to be given every 12 hours	
Plague[4]		
Children ≥ 50 kg	500 mg once every 24 hours	10 to 14 days
Children < 50 kg and ≥ 6 months old	8 mg/kg body weight per dose (not to exceed 250 mg per dose) to be given every 12 hours	

[1] Sequential therapy (IV to oral) may be instituted at the discretion of the physician.

[2] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit.

[3] The safety of levofloxacin in children for durations of therapy beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in children. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk.

[4] Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis.*

Or, as prescribed by a physician.

Directions for Use, Compatibility and Stability:

- **No further dilution of levofloxacin solution for infusion is necessary.**
- Prior to administration, parenteral drug products should be inspected visually for particulate matter and discoloration whenever solution and container permit.
- Observe strict aseptic technique when inserting the cannula of the infusion set into the spout of levofloxacin solution for infusion. If contaminated, it has the potential to become a source of infection to patients. The cannula of the infusion set should be inserted fully and not halfway into the spout of the levofloxacin solution for infusion container to avoid leakage.
- Since only limited data are available on the compatibility of levofloxacin solution for infusion with other IV substances, **additives or other medications should not be added to levofloxacin IV or infused simultaneously through the same IV line.** If the same IV line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of levofloxacin IV with an infusion solution compatible with levofloxacin IV and with any other drugs administered via this common line.
- Levofloxacin solution should not be mixed with heparin or alkaline solution (e,g., sodium bicarbonate, etc.)
- Levofloxacin solution for infusion should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same IV line.
- Levofloxacin solution for infusion is for **single-use only**; any unused portion should be discarded properly.
- Levofloxacin solution should be used within 3 hours after rubber stopper opening in order to prevent bacterial contamination.

CONTRAINDICATIONS

- Known hypersensitivity to levofloxacin, or other quinolones or to any component of the product

WARNINGS AND PRECAUTIONS

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 levofloxacin in patients with known history of myasthenia gravis.

- ***Tendinopathy and Tendon Rupture:*** Fluoroquinolones including levofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. This risk is further increased in those over 60 years old, in kidney, heart, or lung transplant recipients, and with concomitant steroid therapy. Strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis may also increase the risk of tendon rupture. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Levofloxacin should be discontinued if the patient experiences pain, swelling, inflammation, or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their doctor about changing to a non-quinolone antimicrobial drug.
- ***Myasthenia gravis:*** Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing reports of serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Levofloxacin should be avoided in patients with known history of myasthenia gravis.
- ***Hepatotoxicity:*** Severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients treated with levofloxacin. Most cases of severe hepatotoxicity occurred within 6 to 14 days of initiation of levofloxacin therapy and were not associated with hypersensitivity reactions. The majority of fatal cases occurred in patients ≥ 65 years old.

  Levofloxacin should be discontinued in any patient who experiences loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin or eyes, light colored bowel movement, or dark colored urine.
- ***Hypersensitivity:*** Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving fluoroquinolones, including levofloxacin. These reactions often occur after the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, larynx, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, IV fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.
- ***Other Serious and Sometimes Fatal Reactions:*** Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving treatment with fluoroquinolones, including levofloxacin. Clinical manifestations which may be severe and generally occur after multiple doses may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis, including acute hepatitis; jaundice; acute hepatic necrosis or failure; anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

  Levofloxacin should be discontinued immediately at the first appearance of skin rash or any other sign of hypersensitivity and supportive measures instituted.
- ***Central Nervous System (CNS) Disorders:*** Convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones, including levofloxacin. Fluoroquinolones may also cause CNS stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, anxiety, and rarely, suicidal thoughts or acts. These reactions may occur after the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with known or suspected CNS disorders (e.g., severe cerebral arteriosclerosis, epilepsy), or other risk factors (e.g., certain drug therapy, renal impairment) that may predispose to seizures or lower the seizure threshold.

  Levofloxacin should be used with caution in patients with unstable psychiatric illness.
- ***Peripheral Neuropathy:*** 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 fluoroquinolones, including levofloxacin. Symptoms may occur soon after initiation of levofloxacin and may be irreversible. Levofloxacin should be discontinued immediately 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.
- ***Cardiac Disorders:*** Prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia have been reported with some fluoroquinolones, including levofloxacin. Rare cases of *torsades de pointes* have been spontaneously reported during post-marketing surveillance in patients receiving levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, significant bradycardia, cardiomyopathy, or myocardial ischemia. The risk of arrhythmias may be reduced by avoiding concomitant use with other drugs that prolong the QT interval including macrolide antibiotics, antipsychotics, tricyclic antidepressants, class IA (quinidine, procainamide) or class III (amiodarone, sotalol) antiarrhythmic agents, and cisapride. Elderly patients generally may be more susceptible to drug-associated effects on the QT interval.
- ***Clostridium difficile-associated diarrhea (CDAD):*** This has been observed with the use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea following administration of antibacterial agents.
- ***Musculoskeletal Disorders in Children:*** Levofloxacin is indicated in children ≥ 6 months old only for the prevention of inhalational anthrax (post-exposure) and for plague. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin.

510 mm

92.5 mm

185 mm

Pantone Black

• ***F.A. Revision Date: 24 April 2019***

INGRAFIX DESIGN STUDIO

• LEVOX 750 mg/150 mL Intravenous Infusion Package Insert (Back) V. 2

Oral and IV administration of levofloxacin in immature rats and dogs increased the incidence and severity of osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species.

- ***Blood Glucose Disturbances:*** As with other fluoroquinolones, 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., glibenclamide) or with insulin. Careful monitoring of blood glucose is recommended in these patients. Levofloxacin should be discontinued and appropriate therapy initiated immediately if a hypoglycemic reaction occurs. Serious hypoglycemia and hyperglycemia have also occurred in patients without a history of diabetes.

- ***Patients with Glucose-6-phosphate dehydrogenase deficiency:*** Use with caution in patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity who may be prone to hemolytic reactions when treated with fluoroquinolones.

- ***Photosensitivity/Phototoxicity:*** Moderate to severe photosensitivity/ phototoxicity reactions manifesting as exaggerated sunburn reaction have been observed in patients exposed to direct sunlight or ultraviolet (UV) light while receiving fluoroquinolones; hence, direct exposure to excessive sunlight or UV radiation should be avoided during treatment. Therapy should be discontinued if photosensitization occurs.

- ***IV Administration:*** **Since rapid or bolus IV injection may result in hypotension, Levofloxacin 750 mg/150 mL injection should only be administered by slow IV infusion over a period of 90 minutes.**

Other Precautions

- As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during treatment.

- 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.

- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

DRUGS	NATURE OF INTERACTION
Chelation Agents: Antacids, Sucralfate, Didanosine, Metal Cations, Multivitamins	Concomitant administration of levofloxacin tablets with antacids containing calcium, magnesium, or aluminum, as well as sucralfate, didanosine, metal cations such as iron, and multivitamin preparations with zinc, or any products containing any of these components may interfere with the GI 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 therapy.
Anti-arrhythmic Agents	Levofloxacin should be avoided in patients receiving class IA (e.g., quinidine, procainamide) or class III (e.g., amiodarone, sotalol) antiarrhythmic agents because of potential pharmacologic interaction (additive effects on QT interval prolongation).
Antidepressants	Potential pharmacologic interaction with fluoxetine or imipramine (additive effect on QT interval prolongation)
Antidiabetic agents	Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Careful monitoring of blood glucose is recommended when these agents are co-administered.
Ciclosporin and Tacrolimus	Possible pharmacokinetic interactions with ciclosporin or tacrolimus (increased AUC of the immunosuppressive agent). Although no dosage adjustment is necessary, monitoring of plasma concentrations of the immuno-suppressive agent is recommended during concomitant therapy.
Corticosteroids	Risk of tendon rupture during treatment with levofloxacin may be increased in patients receiving corticosteroids, particularly in elderly patients.
Digoxin	There are no significant effects noted during concomitant therapy, therefore, no dosage adjustment is required.
Fluconazole	Both levofloxacin and fluconazole can prolong the QT interval. The simultaneous use of IV levofloxacin and fluconazole resulted in an episode of *torsades de pointes* in a patient on hemodialysis.
Non-steroidal anti-inflammatory drugs (NSAIDs)	Concomitant administration of an NSAID with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.
Probenecid and Cimetidine	Potential pharmacokinetic interaction (increased levofloxacin AUC and $t_{1/2}$) - not considered clinically important; dosage adjustments are not required.
Theophylline	Concomitant administration of other quinolones with theophylline has resulted in prolonged elimination $t_{1/2}$, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions. Closely monitor serum theophylline levels and adjust theophylline dosage accordingly; consider that adverse theophylline effects (e.g., seizures) may occur with or without elevated theophylline concentrations.
Warfarin	There have been reports of enhanced effects of warfarin when co-administered with levofloxacin. Therefore, prothrombin time, International Normalization Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly. Patients should also be monitored for evidence of bleeding.
Zidovudine	Levofloxacin absorption and disposition in HIV-infected subjects, with or without concomitant zidovudine treatment, were similar. The effect of levofloxacin on zidovudine pharmacokinetics has not been studied. No dosage adjustment for levofloxacin appears to be required when co-administered with zidovudine.

Interference with Laboratory Tests

- Some fluoroquinolones, including levofloxacin, may give false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screen by more specific methods may be necessary.

- Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis*, and therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

STATEMENT ON USAGE FOR HIGH RISK GROUPS

Pregnancy: (Pregnancy Category C). There are no adequate and well-controlled studies using levofloxacin in pregnant women. Since levofloxacin, as with most other fluoroquinolones, causes arthropathy in immature animals, the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see **WARNINGS AND PRECAUTIONS**).

Lactation: Levofloxacin has not been measured in human milk. However, based on the ofloxacin data, it can be presumed that levofloxacin will be excreted in human milk. Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother as well as the possible serious adverse effects to the infant.

Children: Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species (see **WARNINGS AND PRECAUTIONS**).

Levofloxacin is indicated in pediatric patients ≥ 6 months old, for inhalational anthrax (post-exposure) and for the treatment of plague, including pneumonic and septicemic plague due to *Yersinia pestis* and prophylaxis for plague. The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate.

Safety and effectiveness in pediatric patients <6 months old have not been established.

Elderly: No dosage adjustment is necessary for elderly patients with normal renal function. However, since levofloxacin is substantially excreted by the kidneys and some elderly patients experience age-related reduction in renal function, care should be taken in dose selection and renal function monitoring is
recommended.

Elderly patients are at increased risk of developing severe tendon disorders including tendon rupture, fatal hepatotoxicity, or prolonged QT interval leading to ventricular arrhythmias when being treated with a
fluoroquinolone such as levofloxacin (see **WARNINGS AND PRECAUTIONS**).

Renal Impairment: Since clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with renal impairment (creatinine clearance <50 mL/min), adjustment of the dosage regimen in such patients is necessary to avoid drug accumulation (see **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: Pharmacokinetic studies in patients with liver impairment 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.

Effects on Ability to Drive and Use Machines: Since there is a potential for levofloxacin to cause dizziness and lightheadedness, patients should be advised to avoid performing tasks which require complete mental alertness such as driving and operating machinery until effects of drug to the individual are known.

UNDESIRABLE EFFECTS

The most common adverse reactions reported with the use of levofloxacin include nausea, vomiting, diarrhea, constipation, headache, insomnia, and dizziness

The following undesirable effects of potential medical importance have occurred in patients receiving levofloxacin, regardless of relationship to the drug:

Body as a Whole: Allergic reaction, asthenia, edema, fever/pyrexia, injection/infusion site reaction (pain, reddening, inflammation), multiple organ failure, pain (including pain in back, chest, and extremities), syncope

Dermatologic/Hypersensitivity Reactions: anaphylactic/anaphylactoid reactions, anaphylactic shock, angioneurotic edema, bullous eruption (including Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme), leukocytoclastic vasculitis, photosensitivity/phototoxicity, pruritus, genital pruritus, rash serum sickness, urticaria

Nervous System: Abnormal dreaming/dreams, abnormal electroencephalogram (EEG), abnormal gait, agitation, amnesia, anorexia, anxiety, confusion, convulsions (seizures), depression, dysphonia, encephalopathy, extrapyramidal symptoms and other disorders of muscular coordination; hallucination, hyperkinesia, hypertonia, exacerbation of myasthenia gravis; nervousness, nightmare, paranoia, paresthesia, sensory or sensorimotor peripheral neuropathy, pseudotumor cerebri, psychosis, sleep disorders, somnolence, isolated reports of suicide attempts or suicidal ideation; tremor, vertigo

Cardiovascular: cardiac failure/arrest, electrocardiogram QT prolonged, palpitation, phlebitis, tachycardia, vasculitis, vasodilatation, ventricular tachycardia, *torsades de pointes*, ventricular arrhythmia

Respiratory: allergic pneumonitis, apnea, dyspnea, laryngeal edema, interstitial pneumonia

Gastrointestinal (GI): Abdominal pain, hemorrhagic diarrhea which in very rare cases may be indicative of enterocolitis including CDAD and colitis; dyspepsia, esophagitis, gastritis, gastroenteritis, GI hemorrhage, glossitis, pancreatitis, stomatitis

Metabolic and Nutritional Disorders: hyperglycemia, hypoglycemia, hyperkalemia

Hepatobiliary: Abnormal hepatic function, increased hepatic enzymes [alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT)]; jaundice/severe liver injury, hepatic failure (including fatal cases), hepatic necrosis, hepatitis

Hematologic: Agranulocytosis, anemia (including aplastic and hemolytic anemia), epistaxis, eosinophilia, granulocytopenia, leukopenia, pancytopenia, prolonged International Normalized Ratio (INR); prolonged prothrombin time; thrombocythemia, thrombocytopenia including thrombotic thrombocytopenic purpura; neutropenia

Genitourinary: Abnormal renal function, acute renal failure, interstitial nephritis, increased blood creatinine; glomerulonephritis, nephrosis, genital moniliasis, vaginitis

Musculoskeletal and Connective Tissue Disorders: Arthralgia, arthritis, increased muscle enzymes; ligament rupture, myalgia, myositis, muscle injury (including rupture), rhabdomyolysis (including fatal cases), skeletal pain, tendinitis/tendinopathy/tendon disorder, tendon rupture

Special Senses: Abnormal vision/visual disturbance including diplopia, reduced visual acuity, blurred vision; scotoma; hearing impairment/hypoacusis, tinnitus; anosmia, parosmia; ageusia, dysgeusia, uveitis

Other Adverse Effects: fungal infection/moniliasis

In clinical trials using multiple dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been observed in patients undergoing treatment with other quinolones.

However, the relationship of the drugs to these events has not been definitely established.

OVERDOSE AND TREATMENT

Clinical features of acute overdosage of levofloxacin may include CNS symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, as well as GI reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. The patient should be observed and proper hydration maintained. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic levofloxacin exposure. Antacids may be used for protection of the gastric mucosa.

Hemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

STORAGE CONDITIONS

- Store in hermetic container at a dry place at temperatures not exceeding 30°C. Protect from light.
- Keep the product out of reach and sight of children.

AVAILABILITY

Levox® 750 mg/ 150 mL Solution for Intravenous Infusion, box x 1 vial

ADVERSE DRUG REACTION REPORTING STATEMENT

For suspected adverse drug reaction, seek medical attention immediately and report to the FDA at www.fda.gov.ph **AND** Unilab at +632-8-**UNILAB-**1 (+632-8-**864522-**1) for Metro Manila or toll-free +1-800-10-UNILAB-1 for provinces, or e-mail productsafety@unilab.com.ph. By reporting undesirable effects, you can help provide more information on the safety of this medicine.

CAUTION

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

Manufactured by:
JEIL PHARMACEUTICAL CO., LTD.
7, Cheongganggachang-ro, Baegam-myeon
Cheoin-gu, Yongin-si, Gyeonggi-do, Republic of Korea
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Metro Manila, Philippines

Trusted Quality Healthcare

Date of First Authorization: July 2018
Date of Revision: October 2018

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WES156899IN01

Reg. IPOPHIL

UNILAB Consumer Care

8-UNILAB-1
8 - 864522 - 1

Provincial Toll Free:+1-800-10-864522-1
E-mail: info@unilab.com.ph
Website: www.unilab.com.ph

510 mm

92.5 mm

185 mm

Pantone Black

• ***F.A. Revision Date: 25 April 2019***