Levofloxacin Hemihydrate

Levox®

500 mg and 750 mg Film-Coated Tablets
250 mg/50 mL Solution for Intravenous Infusion
500 mg/100 mL Solution for Intravenous Infusion

Rx

ANTIBACTERIAL

FORMULATIONS
Each film-coated tablet contains:
Levofloxacin (as hemihydrate) .... 500 mg or 750 mg

Each 50 mL solution for infusion contains:
Levofloxacin (as hemihydrate) ....250 mg

Each 100 mL solution for infusion contains:
Levofloxacin (as hemihydrate) .... 500 mg

PRODUCT DESCRIPTIONS

Levofloxacin (as hemihydrate) (Levox®) 500 mg tablet: is a white, modified, elliptical, film-coated tablet, scored on one side and plain on the other side.

Levofloxacin (as hemihydrate) (Levox®) 750 mg tablet: is an off-white, modified, elliptical, film-coated tablet, bisected on one side and plain on the other side.

Levofloxacin (as hemihydrate) (Levox®) 250 mg/50 mL or 500 mg/100 mL solution for infusion: is a clear greenish yellow solution, free from extraneous matter.

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	*Enterobacter cloacae*
Staphylococcus aureus (methicillin-susceptible strains)	*Escherichia coli*
Staphylococcus epidermidis (methicillin-susceptible strains)	*Haemophilus influenzae*
Staphylococcus saprophyticus	*Haemophilus parainfluenzae*
Streptococcus pneumoniae, including multi-drug resistant strains (MDRSP)	*Klebsiella pneumoniae*
Streptococcus pyogenes	*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	*Acinetobacter baumannii*	*Klebsiella oxytoca*
Streptococcus (Group C/F)	*Acinetobacter lwoffii*	*Morganella morganii*
Streptococcus (Group G)	*Bordetella pertussis*	*Pantoea agglomerans*
Streptococcus agalactiae	*Citrobacter koseri*	*Proteus vulgaris*
Streptococcus milleri	*Citrobacter freundii*	*Providencia rettgeri*
Viridans group streptococci	*Enterobacter aerogenes*	*Providencia stuartii*
*Bacillus anthracis**	*Enterobacter sakazakii*	*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 susceptible tests.

PHARMACOKINETICS

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral/intravenous (IV) dosing regimens. It is rapidly and almost completely absorbed after oral doses with peak plasma concentrations occuring within 1 to 2 hours. Food has little effect on the absorption of levofloxacin. Steady-state conditions are reached within 48 hours after a 500 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.

Levofloxacin is widely distributed into body tissues including the bronchial mucosa and lungs, but penetration into the cerebrospinal fluid is relatively poor. The mean volume of distribution of levofloxacin is approximately 100 L after single and repeated doses. Protein binding is about 30 to 40%.

Levofloxacin is metabolized to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

The elimination half-life of the drug is 6 to 8 hours, although this may be prolonged in patients with renal impairment. Levofloxacin is excreted largely unchanged, primarily in the urine with less than 5% as metabolites. It is not removed by hemodialysis or peritoneal dialysis.

Special Population:

Renal Impairment: Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in patients with impaired renal function (creatinine clearance ≤ 80 mL/min). Dosage adjustment may be required to avoid accumulation.

Hepatic Impairment: Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Geriatrics: There are no significant differences in levofloxacin pharmacokinetics between the young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Drug absorption appears to be unaffected by age. Dose adjustment based on age is not necessary.

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 (SSSI)
- Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections
- Complicated and uncomplicated urinary tract infections (UTIs)
- Acute pyelonephritis
- Chronic bacterial prostatitis

◆ 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 inhalational 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 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 Tablet:

Levofloxacin tablet can be taken with or without food. Administer dose at least 2 hours before or 2 hours after antacids containing calcium, magnesium or aluminum, after sucralfate or metal cations such as iron, multivitamin preparations with zinc, or with didanosine. Concomitant administration with these drugs may significantly decrease levofloxacin absorption.

Usual Recommended Dose: Orally, 500 mg or 750 mg once every 24 hours. The dose and duration of treatment are based on the type and severity of the infection being treated (see **Dosing Table**).

Levofloxacin Solution for Infusion

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: 250 mg or 500 mg administered by slow IV infusion over 60 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 Oral or 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 Oral or 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: $CL_{CR}\ (\text{mL/min}) = \dfrac{\text{Weight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mg/dL)}}$

Women: 0.85 x the value calculated using the above formula

Levofloxacin Oral or IV Dosing in Children:

Infections	Levofloxacin Oral or IV Dose[1]	Duration of Treatment
Inhalation 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 for infusion is compatible with 0.9% Sodium Chloride Solution, 5% Dextrose Injection, 2.5% Dextrose in Ringer's Solution, and combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).
- 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.

CONTRAINDICATION

Known hypersensitivity to levofloxacin, 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.

Methicillin-resistant *Staphylcoccus aureus* (MRSA): Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore, levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

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.

If the diagnosis of CDAD is suspected or confirmed, appropriate therapeutic measures should be initiated. Mild cases of CDAD usually respond to discontinuation of antibacterial agents not directed against *Clostridium difficile*. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial agent clinically effective against *Clostridium difficile*. Surgical evaluation should be instituted as clinically indicated since surgical intervention may be required in certain severe cases.

Tendinitis 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.

Exacerbation of 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.

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.

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.

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 and older.

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 Reactions: 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. 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, 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 in patients receiving therapy 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; 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.

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.

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.

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.

Renal: The risk of toxic reactions to levofloxacin may be greater in patients with impaired renal function since levofloxacin is known to be substantially excreted by the kidney. Adjustment of the dosage regimen may be necessary to avoid the accumulation of levofloxacin due to decreased clearance. Careful observation and appropriate laboratory studies should be done prior to and during therapy, since elimination of levofloxacin may be reduced. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Administer levofloxacin with caution in the presence of renal insufficiency.

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.

Hypoglycemic coma has been observed in diabetic patients on levofloxacin therapy. Fatal outcomes have been reported. All cases of hypoglycemic coma had multiple confounding factors; a temporal relationship with the use of levofloxacin was identified (onset of altered consciousness occurred within 3 days in most cases). Caution should be exercised when using levofloxacin in diabetic patients taking concomitant treatment with an oral hypoglycemic agent and/or insulin, particularly those who are elderly or who have renal impairment.

Patients with G-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.

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.

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.
- Levofloxacin is not indicated for the treatment of syphilis or gonorrhea. Levofloxacin is not effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with antimicrobial agents with limited or no activity against *Treponema pallidum* should have a follow-up serologic test for syphilis after 3 months.
- As with other antibacterial drugs, long term or repeated use may result in overgrowth of non-susceptible organisms, including fungi.

INTERACTIONS WITH OTHER MEDICAMENTS

- **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.
- **Antidepressants (e.g., fluoxetine, imipramine):** Potential pharmacologic interaction with these antidepressants.
- **Chelation Agents (e.g., antacids, sucralfate, metal cations, multivitamins):** Concomitant administration of levofloxacin tablets with antacids containing calcium, magnesium, or aluminum, as well as sucralfate, metal cations such as iron, multivitamin preparations with zinc, or any products containing any of these components may interfere with the gastrointestinal absorption of levofloxacin due to the chelation of levofloxacin by multivalent cations, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin therapy.
- **Ciclosporin:** Elevated serum levels of ciclosporin have been reported when concomitantly used with other quinolones. Levofloxacin peak concentration and elimination rate were slightly lower, while the time at which the peak concentration is achieved and $t_{1/2}$ were slightly longer in the presence of ciclosporin, than those observed in patients without concomitant drug. The differences, however, are not considered to be clinically significant. No dosage adjustment is required for levofloxacin or ciclosporin when administered concomitantly.
- **Corticosteroids:** Concomitant use of corticosteroids increases the risk of severe tendon disorders (e.g., tendinitis, tendon rupture), particularly in elderly patients older than 60 years old.
- **Digoxin:** There are no significant effects noted during concomitant therapy, therefore, no dosage adjustment is required.
- **Nonsteroidal 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.
- **Sucralfate:** The bioavailability of levofloxacin is significantly reduced when concomitantly used with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate two hours after levofloxacin administration.
- **Tacrolimus:** Possible pharmacokinetic interactions with tacrolimus (increased AUC of the immunosuppressive agent). Dosage adjustment is 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. Thus, theophylline levels should be closely monitored, and appropriate dosage adjustments made when levofloxacin is concomitantly used.
- **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 individuals, with or without concomitant zidovudine treatment, were similar. The effect of levofloxacin on zidovudine pharmacokinetics has not been studied. No dosage adjustment for levofloxacin is required when concomitantly used 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 AND LACTATION

Pregnancy Category C. 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: Based on data on other fluoroquinolones and very limited data on levofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in breastfeeding infants, 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.

PEDIATRICS: Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. In a prospective long-term surveillance study, the incidence of protocol-defined musculoskeletal disorders was higher in children treated for approximately 10 days with levofloxacin than in children treated with non-fluoroquinolone antibiotics for approximately 10 days.

GERIATRICS: There is no substantial difference in safety and efficacy relative to younger adults, but increased sensitivity cannot be ruled out.

Risk of severe tendon disorder, including tendon rupture, is increased in older adults, usually those older than 60 years old. This risk is further increased in those receiving concomitant corticosteroids. Caution is advised in geriatric adults, particularly those receiving concomitant corticosteroids.

Risk of fatal hepatotoxicity may be increased in geriatric patients.

Risk of prolonged QT interval leading to ventricular arrhythmias may be increased in geriatric patients, particularly those receiving concurrent therapy with other drugs that can prolong QT interval (e.g., class IA or III antiarrhythmic agents) or with risk factors for torsades de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

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.

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.

UNDESIRABLE EFFECTS

Body as a Whole: Moniliasis, fungal infection including Candida infection, edema, multi organ failure, pyrexia, asthenia, pain (including pain in back, chest, and extremities), injection site reaction

Cardiovascular: Chest pain, cardiac arrest, palpitation, ventricular tachycardia, ventricular arrhythmia, syncope, phlebitis, torsades de pointes, electrocardiogram QT prolonged, tachycardia, vasodilation, vasculitis, benign intracranial hypertension, hypotension

CNS: Insomnia, anxiety, agitation, confusion, depression, hallucination, nightmare, sleep disorder, abnormal dreaming, psychosis, paranoia, isolated reports of suicide attempt and suicidal ideation, headache, dizziness, tremor, convulsions, paresthesia, vertigo, hypertonia, hyperkinesia, abnormal gait, somnolence, peripheral neuropathy (may be irreversible), isolated reports of encephalopathy, abnormal EEG, dysphonia, exacerbation of myasthenia gravis, amnesia, pseudotumor cerebri, nervousness, peripheral sensory neuropathy, peripheral sensory motor neuropathy, dyskinesia, extrapyramidal disorder

Dermatologic and Sensitivity Reactions: Rash; pruritus; urticaria; allergic reaction; angioedema, hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions, anaphylactic shock, angioneurotic edema, serum sickness; bullous eruptions to include: Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity/phototoxicity reaction, leukocytoclastic vasculitis; hyperhidrosis; mucocutaneous reactions

Endocrine and Metabolic: Hyperglycemia, hypoglycemia, hypoglycemic coma, hyperkalemia, anorexia

Gastrointestinal: Nausea, diarrhea, constipation, abdominal pain, vomiting, dyspepsia, gastritis, stomatitis, pancreatitis, esophagitis, gastroenteritis, glossitis, pseudomembranous/*C. difficile* colitis, flatulence

Hepatic: Abnormal hepatic function, increased hepatic enzymes (ALT/AST/CGT), increased alkaline phosphatase, hepatic failure (including fatal cases), hepatitis, jaundice, hepatic necrosis, blood bilirubin increased

Hematologic: Anemia, thrombocytopenia, thrombocytopenia including thrombotic thrombocytopenic purpura, agranulocytosis, granulocytopenia, pancytopenia, aplastic anemia, leukopenia, hemolytic anemia, eosinophilia, neutropenia, prothrombin time prolonged, international normalized ratio (INR) prolonged

Musculoskeletal: Tendon disorder including tendinitis, arthralgia, myalgia, skeletal pain, tendon rupture, muscle injury (including rupture), rhabdomyolysis, myositis, myalgia, ligament rupture, muscle rupture, arthritis, muscle enzymes increased (CPK)

Reproductive/Urogenital System: Vaginitis, genital moniliasis, abnormal renal function, acute renal failure, interstitial nephritis, nephrosis, glomerulonephritis, blood creatinine increased

Respiratory: Dyspnea, epistaxis, allergic pneumonitis, interstitial pneumonia, laryngeal edema, apnea, bronchospasm

Special Senses: Uveitis, vision disturbance (including diplopia), visual acuity reduced, vision blurred, transient vision loss, scotoma, hypoacusis, tinnitus, hearing loss, hearing impaired, anosmia, parosmia, dysgeusia, ageusia

OVERDOSE AND TREATMENT

Clinical features of acute overdosage of levofloxacin may include CNS symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval, 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 at temperatures not exceeding 30°C.

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) 858-1000 or 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.

AVAILABILITY

*Levofloxacin Hemihydrate (Levox®) 500 mg Film-Coated Tablet - Box of 40s (in blister foil)
*Levofloxacin Hemihydrate (Levox®) 750 mg Film-Coated Tablet - Box of 20s (in blister foil)
**Levofloxacin Hemihydrate (Levox®) 250 mg/50 mL Solution for Intravenous Infusion - Box of 1 Vial
**Levofloxacin Hemihydrate (Levox®) 500 mg/100 mL Solution for Intravenous Infusion -Box of 1 Vial

*Manufactured by AMHERST LABORATORIES, INC., UNILAB Pharma Campus
Barangay Mamplasan, Biñan, Laguna, Philippines for **UNILAB, Inc.**
No. 66 United Street, Mandaluyong City, Metro Manila, Philippines
Under License by DAIICHI SANKYO CO., LTD.
3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo, Japan

**Manufactured by AMHERST PARENTERALS, INC., Sta. Rosa-Tagaytay Road
Don Jose, Sta. Rosa City, Laguna, Philippines for **UNILAB, Inc.**
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Levofloxacin Hemihydrate (Levox®)
- 500 mg Film-Coated Tablet: DR-XY23653
- 750 mg Film-Coated Tablet: DR-XY32085
- 250 mg/50 mL Solution for Intravenous Infusion: DR-XY34588
- 500 mg/100 mL Solution for Intravenous Infusion: DR-XY27919

Date of Revision: July 2017
Date of First Authorization:
Levofloxacin Hemihydrate (Levox®)
- 500 mg Film-Coated Tablet: November 2004
- 750 mg Film-Coated Tablet: June 2007
- 250 mg/50 mL Solution for Intravenous Infusion: May 2008
- 500 mg/100 mL Solution for Intravenous Infusion: October 2002

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