Avoxin®

Levofloxacin

DESCRIPTION:
Levofloxacin is a synthetic broad spectrum antibacterial agent for oral and intravenous administration, chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido(1,2,3-de)-1,4-benzoxazine-6-carboxylic acid hemihydrate.

MICROBIOLOGY:
Levofloxacin is the L-islomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. 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 a wide range of gram negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentration equal to or slightly greater than inhibitory concentrations.
Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and B-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.
Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10-9 to 10-10). Although cross resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.
Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the INDICATIONS AND USAGE section:
Aerobic gram-positive microorganisms:
Enterococcus faecalis (many strains are only moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains).
Staphylococcus epidermidis (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including multi-drug resistant strains (MDRSP)•)
Streptococcus pyogenes.
•MDRSP (multi-drug resistance *Streptococcus pneumoniae*) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC > 2 μg/mL), 2nd generation cephalosporins, e.g, cefuroxime, macrolides, tetracyclines and trimethoprim/sulfsmethoxazole.
Aerobic gram-negative microorganisms:
Enterobacter cloacae, Haemophillus parainfluenzae, Moraxella catarrhalis, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Haemophilus influenzae, Legionella pneumophila, Pseudomonas aeruginosa, Serratia marcescens
As with other drugs in this class, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with levofloxacin.
Other microorganisms
Chlamydia pneumoniae
Mycoplasma pneumoniae
Levofloxacin has been shown to be active against Bacillus anthracis both in vitro and by use of plasma levels as a surrogate maker in a rhesus monkey model for anthrax (post-exposure).
The following in vitro data are available, but their clinical significance is unknown.
Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 μg/ml or less against most (>90%) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.
Aerobic gram-positive microorganisms: ***Staphylococcus haemolyticus, Streptococcus*** **(Group C/F),** ***Streptococcus*** **(Group G),** ***Streptococcus agalactiae, Streptococcus milleri, Viridans group streptococci.***
Aerobic gram-negative microorganisms: ***Acinetobacter baumannii, Acinetobacter lwoffii, Bordetella pertussis, Citrobacter freundii, Enterobacter aerogenes, Enterobacter sakazakii, Klebsiella oxytoca, Morganella morganii, Pantoea*** **(*Enterobacter*)** ***agglomerans, Proteus vulgaris, Providencia rettgeri, Citrobacter*** **(*diversus*)** ***koseri, Providencia stuartii, Pseudomonas fluorescens.***
Anaerobic gram-positive microorganisms: ***Clostriduim perfringens***

INDICATIONS AND USAGE:
To reduce the development of drug-resistant bacteria and maintain the effectiveness of **Avoxin®** (levofloxacin) and other antibacterial drugs, levofloxacin should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
Avoxin® Tablets are 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.
Acute bacterial sinusitis due to ***Streptococcus pneumonia, Haemophilus influenzae*** **or** ***Moraxella catarrhails.***
Acute bacterial exacerbation of chronic bronchitis due to ***Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis.***
Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, klebsiella pneumoniae, Haemophilus influenzae* or *Streptococcus pnenumonia* adjunctive therapy should be used as clinically indicated. Where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an antipseudomonal B-lactam is recommended
Community-acquired pneumonia due to ***Staphylococcus aureus, Streptococcus pneumoniae*** (including multi-drug-resistant strains (MDRSP)•, ***Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhails, Chlamydia pneumoniae, Legionella pneumophilla or Mycoplasma pneumoniae.***
•MDRSP (multi-drug resistant Streptococcus pneumoniae) isolates are strains resistant to two or more of the following antibiotics: penicillin (MIC >2 μg/mL), 2nd generation cephalosporins, e.g: cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.
Complicated skin and skin structure infections due to methicillin-susceptible ***Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes,*** or ***Proteus mirabilis.***
Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to ***Staphylococcus aureus,*** or ***Streplococcus pyogenes.***
Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or *Staphylococcus epidermidis.*
Complicated urinary tract infections (mild to moderate) due to ***Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,*** or ***Pseudomonas aeruginosa.***
Acute pyelonephritis (mild to moderate) caused by ***Escherichia coli.***
Uncomplicated urinary tract infections (mild to moderate) due to ***Escherichia coli, Klebsiella pneumoniae,*** or ***Staphylococcus saprophyticus.***
Inhalational anthrax (post-exposure) To prevent the development of inhalational anthrax following exposure to *Bacillus anthracis* (See DOSAGE AND ADMINISTRATION and ADDITIONAL INFORMATION-INHALATIONAL ANTHRAX).
Levofloxacin has not been tested in human for the post-exposure prevention of inhalational anthrax. However, plasma concentrations achieved in humans are reasonably likely to predict efficacy.
Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to Levofloxacin. Therapy with Levofloxacin may be initiated before results of these tests are known, once results become available, appropriate therapy should be selected.
As with other drugs in this class, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with Levofloxacin, Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS:
Levofloxacin is contraindicated in persons with a history of hypersensitivity to Levofloxacin or quinolone antibacterial agents.

WARNINGS:
THE SAFETY EFFICAY OF LEVOFLOXACIN IN PEDIATRIC, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See PRECAUTIONS. Pediatric Use, Pregnancy, and Nursing Mothers subsections)
In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased 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 erosion in the weight bearing joints and other signs of arthropathy in immature animals of various species. The relevance of these findings to the clinical use of levofloxacin is unknown. Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. Theses reactions may occur following 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 a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g, certain drug therapy, renal dysfunction.) (See PERCAUTIONS and ADVERSEREACTIONS)
Serious and occasionally fatal 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 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. (See PERCAUTIONS and ADVERSEREACTIONS).
Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be serve and generally occur following the administration of multiple doses. Clinical manifestations 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. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See PRECAUTIONS: Information for patients and ADVERSE REACTIONS.)
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 has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. 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 agent 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. (See adverse reactions).
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.

PRECAUTIONS:
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.
Although levofloxacin is more soluble than other quinolones, adequate hydration of patient 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 <50 mL/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 photoxicity (e.g., skin eruption) occurs. As with other quinolones, levofloxacin should be used with caution in any patient wih a known or suspected CNS disorder that may predispose to seizure or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizure threshold (e.g, certain drug therapy, renal dysfunction). (See WARNINGS and DRUG INTERACTIONS).
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 hypoglycemia 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. (See DRUG INTERACTIONS and ADVERSE REACTIONS).
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. (See WARNINGS and ADVERSE REACTIONS.)
Information for Patients:
Patients should be advised:
• Patients should be counseled that antibacterial drugs including Levofloxacin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When Levofloxacin 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 (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria well develop resistance and will not be treatable by Levofloxacin 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 didanosine should be taken at least two hours before or two hours after oral levofloxacin administration. (See DRUG INTERACTIONS);
• 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 thay react to levofloxacin before they operate and automobile or machinery or engage in other activities requiring mental alertness and coordination. (See WARNINGS and ADVERSE REACTIONS);
• 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 tendonitis or tendon rupture ha been confidently excluded;
• that levofloxacin may be associated with hypersensitivity reactions, even following tha 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. (See WARNINGS and ADVERSE REACTIONS);
• 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. (See PRECAUTIONS: General and Drug Interactions);
• 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.
Drug Interactions:
Antacids, Sucralfate, Metal Cations, Multivitamins:
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 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.
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. (See WARNINGS and PRECAUTIONS: General.)
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 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 Cmax and Ke were slightly lower while Tmax and t1/2 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 Probenecid or Cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and t1/2 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. (See WARNINGS and PRECAUTIONS: General.)
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 theses agents are co-administered.
Interaction with Laboratory or Diagnostic Testing: Some quinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.
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 (100 mg/kg/day) was 14 times the highest recommended human dose (750 mg) 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 42 μg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg levofloxacin averaged approximately 11.8 μg/g at Cmax.

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 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.
Pregnancy: Teratogenic Effects. Pregnancy Category C.
Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 94 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.
There are, however, 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. (See WARNINGS.)
Nursing Mothers
Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, 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.
Pediatric Use
Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNINGS.)
Geriatric Use
It was reported in clinical trials, 1,190 levofloxacin-treated patients (25%) were >65% years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 patients (11%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.
Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsades de points (e.g. known QT prolongation, uncorrected hypokalemia). (See PRECAUTIONS: GENERAL: Torsades de points).
The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. 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.

ADVERSE REACTIONS:
The incidence of drug-related adverse reactions in patients during clinical trials conducted in North America was 6.7%. Among patients receiving levofolxacin therapy, 4.1% discontinued levofloxacin therapy due to adverse experiences.
In all clinical trials, the overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily.
In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin:
nausea 1.5%, diarrhea 1.2%, vaginitis 0.5%, insomnia 0.4%, abdominal pain 0.4%, flatulence 0.2%, pruritus 0.2%, dizziness 0.3%, rash 0.3%, dyspepsia 0.3%, genital moniliasis 0.1%, moniliasis 0.2%, taste perversion 0.2%, vomiting 0.3%, constipation 0.1%, fungal infection 0.1%, genital pruritis 0.1%, headache 0.2%, nervousness 0.1%, rash erythematous 0.1%, urticaria 0.1%, anorexia 0.1%, somnolence 0.1%, agitation 0.1%, rash maculo-papular (<0.1%), dry mouth 0.2%, tremor 0.1%, condition aggravated 0.1%, allergic reaction 0.1%.
In clinical trials, the following events occurred in > 3% of patients, regardless of drug relationship:
Nausea 6.8%, headache 5.8%, diarrhea 5.4%, insomnia 4.6%, constipation 3.1%.
In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:
Abdominal pain 2.5%, dizziness 2.4%, vomiting 2.4%, dyspepsia 2.3%, vaginitis 1.3%, rash 1.4%, chest pain 1.2%, pruritis 1.2%, sinusitis 1.1%, dyspnea 1.3%, fatigue 1.2%, flatulence 1.2%, pain 1.3%, back pain 1.2%, rhinitis 1.2%, pharyngitis 1.1%.
In clinical trials, the following events, of potential medical importance, occurred at rate of 0.1% to 0.9%, regardless of drug relationship:
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 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, temor, 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
Neoplasmas: 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 (Extracadiac) Disorders: Flushing, cerebrovascular disorder, gangrene, phlebitis, purpura, thrombophlebitis (deep)
Vision Disorders: Abnormal vision, eye pain, conjuctivitis
White Cell and RES Disorders: Agranulocytosis, granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal NOS
In clinical trials using multiple-dose therapy, ophthalmologic, abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones. The relationship of the drugs to these events is not presently established.
Crystalluria and cylindruria have been reported with other quinolones.
The following markedly abnormal laboratory values appeared in >2% of patients receiving levofloxacin. It is not known whether this abnormality was caused by the drug or the underlying conditions being treated.
Hematology: decreased lymphocytes (2.2%)
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.

OVERDOSAGE:
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 1500 mg/kg orally and 250 mg/kg i.v. produced significant mortality in rodents. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION:
The usual dose of levofloxacin Tablets 250 mg or 500 mg or 750 mg administered orally every 24 hours, as indicated by infection and described in the following dosing chart. Levofloxacin tablets can be administered without regard to food. These recommendations apply to patients with normal renal function (i.e., creatinine clearance>80 ml/min). For patients with altered renal function see the Patients with Impaired Renal Function subsection. Oral doses should be administered at least two hours before or two hours after antiacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamins preparations with zinc or didanosine, chewable/buffered tablets or the pediatric powder for oral solution.

Patients with Normal Renal Function

Infection1	Unit Dose	Freq.	Duration2	Daily Dose
Comm. Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Comm. Acquired Pneumonia	750 mg3	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) Adults4,5	500 mg	q24h	60 days5	500 mg

1DUE TO THE DESIGNATED PATHOGENS (See INDICATIONS AND USAGE)
2Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
3Efficacy of this alternative regimen has been demonstrated to be effective for infections caused by *Streptococcus pneumoniae* (excluding MDRSP), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae and Chlamydia pneumoniae.*
4Drug 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.
5The safety of levofloxacin in adults for durations of therapy beyond 28 days has not been studied. Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the risk.

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}>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:

$$\text{Mean Creatinine Clearance (ml/min)} = \frac{\text{Weight (kg)} \cdot (140\text{-age})}{72 \cdot \text{serum creatinine (mg/dl)}}$$

Women: 0.85• the value calculated for men.
The serum creatinine should represent a steady state of renal function.

Patient Information About:
Avoxin® (levofloxacin) Tablets 250 mg Tablets, 500 mg Tablets, and 750 mg Tablets
This leaflet contains important information about Avoxin® (levofloxacin), and should be read completely before you begin treatment. This leaflet dose not take the place of discussions with your doctor or health care professional about your medical condition or your treatment. This leaflet does not list all benefits and risks of Levofloxacin. The medicine described here can be prescribed only by a licensed health care professional. If you have any questions about **Avoxin®** talk to your health care professional. Only your health care professional can determine if Avoxin® is right for you.
What is Avoxin®?
Avoxin® is a quinolone antibiotic used to treat lung, sinus, skin, and urinary tract infections caused by certain germs called bacteria. Avoxin® kills many of the types of bacteria that can infect the lungs, sinuses, skin, and urinary tract and has been shown in a large number of clinical trials to be safe and effective for the treatment of bacterial infections.
Sometimes viruses rather than bacteria may infect the lungs and sinuses (for example the common cold). Levofloxacin, like other antibiotics, does not kill viruses.
You should contact your health care professional if you think that your condition is not improving while taking Levofloxacin
How and when should I take Avoxin®?
Levofloxacin should be taken once a day for 3, 5, 7, 10, 14 or 28 days depending on your prescription. Avoxin® Tablets should be swallowed and may be taken with or without food. Try to take the tablet at the same time each day and drink fluids liberally.
You may begin to feel better quickly, however, in order to make sure all bacteria are killed, you should complete the full course of medication. Do not take more than the prescribed dose of Levofloxacin even if you missed a dose by mistake. You should not take a double dose.
Who should not take Levofloxacin?
You should not take Levofloxacin if you have ever had a serve allergic reaction to any of the group of antibiotics known as "quinolones" such as ciprofloxacin. Serious and occasionally fatal allergic reactions have been reported in patients receiving therapy with quinolones, including Levofloxacin.
If you are pregnant or are planning to become pregnant while taking Levofloxacin, talk to your health care professional before taking this medication. Levofloxacin is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.
Levofloxacin is not recommended for children.
What are possible side effects of Levofloxacin?
Levofloxacin is generally well tolerated. The most common side effects caused by Levofloxacin, which are usually mild, include nausea, diarrhea, itching, abdominal pain, dizziness, flatulence, rash and vaginitis is women.
You should be careful about driving or operating machinery until you are sure Levofloxacin is not causing dizziness.
Allergic reactions have been reported in patients receiving quinolones including Levofloxacin, even after just one dose. If you develop hives, skin rash or other symptoms of an allergic reaction, you should stop taking this medication and call your health care professional.
Ruptures of shoulder, hand, or Achilles tendons have been reported in patients receiving quinolones, including Levofloxacin. If you develop pain, swelling, or rupture of tendon you should stop taking Levofloxacin and contact your health care professional.
Some quinolone antibiotics have been associated with the development of phototoxicity ("sunburns" and blistering sunburns") following exposure to sunlight or other sources of ultraviolet light such as artificial ultraviolet light used in tanning salons. Levofloxacin has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking Levofloxacin.
If you have diabetes and you develop a hypoglycemic reaction while on Levofloxacin, you should stop taking Avoxin® and call your health care professional.
Convulsions have been reported in patients receiving quinolone antibiotics including Levofloxacin. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.
Quinolones, including Levofloxacin, may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, suicidal thoughts or acts.
If you notice any side effects not mentioned in this leaflet or you have concerns about the side effects you are experiencing, please inform your health care professional.
For more complete information regarding levofloxacin, please refer to the full prescribing information which may be obtained from your health care professional or pharmacist.
What about other medicines I am taking?
Taking warfarin and Levofloxacin together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your health care professional. Many antacids and multivitamins may interfere with the absorption of levofloxacin and may prevent it from working properly. You should take **Avoxin®** either 2 hours before or 2 hours after taking these products.
It is important to let your health care professional know all of the medicines you are using.
Other information
Take your dose of **Avoxin®** once a day.
Complete the course of medication even if you are feeling better. Keep this medication out of the reach of children.
Some quinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.
This information does not take the place of discussions with your doctor or health care professional about your medical condition your treatment.
PRESENTATION:
Avoxin® 750: each pack contains 7 tablets. **Avoxin®** 500: each pack contains 7 tablets. **Avoxin®** 250: each pack contains 7 tablets.

Avoxin®

Levofloxacin

• A medicament is a product that affects your health, and its consumption contrary to instructions is dangerous for you.
• Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who dispensed the medicament.
• The doctor and the pharmacist are experts in medicine.
• Do not by yourself interrupt the period of treatment prescribed for you.
• Do not repeat the same prescription without consulting your doctor.
• Keep medicaments out of the reach of children.

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UNION OF ARAB PHARMACISTS

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