

VOLOXAL

Tablets

Composition

each tablet contains levofloxacin 500 & 750 mg

Action

Bactericidal; as a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-gyrase complex and topoisomerase IV needed for the synthesis of bacterial DNA . Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents .

Antibacterial spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species
<u>Aerobic Gram-positive bacteria</u> Staphylococcus aureus* methicillin-susceptible Staphylococcus saprophyticus Streptococci, group C and G <i>Streptococcus agalactiae</i> <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> *
<u>Aerobic Gram- negative bacteria</u> <i>Burkholderia cepacia</i> § <i>Eikenella corrodens</i> <i>Haemophilus influenzae</i> * <i>Haemophilus para-influenzae</i> * <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> * <i>Moraxella catarrhalis</i> * <i>Pasteurella multocida</i> <i>Proteus vulgaris</i> <i>Providencia rettgeri</i>
<u>Anaerobic bacteria</u> <i>Peptostreptococcus</i>
<u>Other</u> <i>Chlamydophila pneumoniae</i> * <i>Chlamydophila psittaci</i> <i>Chlamydia trachomatis</i> <i>Legionella pneumophila</i> * <i>Mycoplasma pneumoniae</i> * <i>Mycoplasma hominis</i> <i>Ureaplasma urealyticum</i>
Species for which acquired resistance may be a problem
<u>Aerobic Gram-positive bacteria</u> <i>Enterococcus faecalis</i> * Staphylococcus aureus methicillin-resistant Coagulase negative Staphylococcus spp
<u>Aerobic Gram- negative bacteria</u>

Acinetobacter baumannii *
Citrobacter freundii *
Enterobacter aerogenes
Enterobacter agglomerans
Enterobactercloacae *
Escherichia coli *
Morganella morganii *
Proteus mirabilis *
Providencia stuartii
Pseudomonas aeruginosa *
Serratia marcescens *

Anaerobic bacteria
Bacteroides fragilis
Bacteroides ovatus §
Bacteroides thetaiotamicron §
Bacteroides vulgatus §
Clostridium difficile §

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

§ Natural intermediate susceptibility

+ More than 50% of resistance

Other information

Nosocomial infections due to *P. aeruginosa* may require combination therapy.

Pharmacokinetics

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is approximately 100 %.

Food has little effect on the absorption of levofloxacin.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

Penetration into tissues and body fluids:

Penetration into Bronchial Mucosa, Epithelial Lining Fluid (ELF)

Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after 500 mg p.o. were 8.3 µg/g and 10.8 µg/ml respectively. These were reached approximately one hour after administration.

Penetration into Lung Tissue

Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 µg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.

Penetration into Blister Fluid

Maximum levofloxacin concentrations of about 4.0 and 6.7 µg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily, respectively.

Penetration into Cerebro-Spinal Fluid

Levofloxacin has poor penetration into cerebro-spinal fluid.

Penetration into prostatic tissue

After administration of oral 500mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7 µg/g, 8.2 µg/g and 2.0 µg/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

Concentration in urine

The mean urine concentrations 8 -12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively.

Biotransformation

Levofloxacin is metabolised 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.

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{1/2}$: 6 - 8 h). Excretion is primarily by the renal route > 85 % of the administered dose). There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Cl _{cr} [ml/min]	< 20	20 - 40	50 - 80
Cl _R [ml/min]	13	26	57
T _{1/2} [h]	35	27	9

Elderly subjects

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences

Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

Indications

In adults with infections of mild or moderate severity, Voloxal tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated urinary tract infections including pyelonephritis
- Chronic bacterial Prostatitis.
- Skin and soft tissue infections.

Before prescribing Voloxal, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

Contraindications

- In patients hypersensitive to levofloxacin or other quinolones or any of the excipients,
- In patients with epilepsy,

- In patients with history of tendon disorders related to fluoroquinolone administration,
- In children or growing adolescents,
- During pregnancy,
- In breast-feeding women.

Warnings & Precautions

- May exacerbate muscle weakness in persons with myasthenia gravis. Avoid use in patients with a known history of myasthenia gravis.
- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose.
- Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses.
- Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur.
- Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold.
- *Clostridium difficile*-associated colitis: evaluate if diarrhea occurs.
- Peripheral neuropathy: discontinue if symptoms occur in order to prevent irreversibility.
- Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval.

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. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. 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 healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Pregnancy

Category C

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Nursing Mothers

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 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.

Adverse Reactions

The information given below is based on data from clinical studies in more than 5000 patients and on extensive post marketing experience.

The adverse reactions are described according to the MedDRA system organ class below. Frequencies are defined using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $\leq 1/100$), rare ($\geq 1/10000$, $\leq 1/1000$), very rare ($\leq 1/10000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Fungal infection (and proliferation of other resistant microorganisms)

Blood and lymphatic system disorders

Uncommon: Leukopenia, eosinophilia

Rare: Thrombocytopenia, neutropenia

Very rare: Agranulocytosis

Not Known: Pancytopenia, haemolytic anaemia

Immune system disorders

Very rare: Anaphylactic shock

Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

Not known: Hypersensitivity

Metabolism and nutrition disorders

Uncommon: Anorexia

Very rare: Hypoglycemia, particularly in diabetic patients

Psychiatric disorders

Uncommon: Insomnia, nervousness

Rare: Psychotic disorder, depression, confusional state, agitation, anxiety

Very rare: Psychotic reactions with self-endangering behavior including suicidal ideation or acts, hallucination

Nervous system disorders

Uncommon: Dizziness, headache, somnolence

Rare: Convulsion, tremor, paraesthesia

Very rare: sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

Eye disorders

Very rare: Visual disturbance

Ear and Labyrinth disorders

Uncommon: Vertigo

Very rare: Hearing impaired

Not known: Tinnitus

Cardiac disorders

Rare: Tachycardia

Not Known: Electrocardiogram QT prolonged

Vascular disorders

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm, dyspnoea

Very rare: Pneumonitis allergic

Gastrointestinal disorders

Common: Diarrhoea, nausea

Uncommon: Vomiting, abdominal pain, dyspepsia, flatulence, constipation.

Rare: Diarrhoea –haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

Hepatobiliary disorders

Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)

Uncommon: Blood bilirubin increased

Very rare: Hepatitis

Not known: Jaundice and severe liver injury, including cases with liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases

Skin and subcutaneous tissue disorders

Uncommon: Rash, pruritus

Rare: Urticaria

Very rare: Angioneurotic oedema, photosensitivity reaction

Not Known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis. Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and Connective tissue disorders

Rare: Tendon disorder including tendinitis (e.g. Achilles tendon), Arthralgia, Myalgia

Very rare: Tendon ruptures. This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis

Not Known: Rhabdomyolysis

Renal and urinary disorders

Uncommon: Blood creatinine increased

Very rare: Renal failure acute (e.g. due to nephritis interstitial)

General disorders and administration site conditions

Uncommon: Asthenia

Very rare: Pyrexia

Not known: Pain (including pain in back, chest, and extremities)

Other undesirable effects which have been associated with fluoroquinolone administration include:

- Extrapyramidal symptoms and other disorders of muscular coordination,
- Hypersensitivity vasculitis,
- Attacks of porphyria in patients with porphyria.

Drug Interactions

Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

While the chelation by divalent cations is less marked than with other fluoroquinolones, concurrent administration of Levofloxacin Tablets and Oral Solution 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 oral Levofloxacin administration.

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. However, there have been reports during the post marketing experience in patients that Levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and Levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if Levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding.

Antidiabetic Agents

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

Non-Steroidal Anti-Inflammatory Drugs

The concomitant administration of a non-steroidal anti-inflammatory drug with a fluoroquinolone, including Levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

Theophylline

No significant effect of Levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones 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.

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 fluoroquinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{1/2}$ 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 of probenecid or cimetidine on the C_{max} of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and $t_{1/2}$ of levofloxacin were higher while CL/F and CLR were lower during concomitant treatment of Levofloxacin with probenecid or cimetidine compared to Levofloxacin alone. However, these changes do not warrant dosage adjustment for Levofloxacin when probenecid or cimetidine is co-administered.

Interactions with Laboratory or Diagnostic Testing

Some fluoroquinolones, 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.

Dosage and Administration

The usual dose of Voloxal Tablets is 500 mg or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1. These recommendations apply to patients with creatinine clearance \geq 50 mL/min.

Table 1: Dosage in Adult Patients with Normal Renal Function (creatinine clearance \geq 50 mL/min)

Type of Infection*	Dosed Every 24 hours	Duration (days)
Nosocomial Pneumonia	750 mg	7-14
Community Acquired Pneumonia [‡]	500 mg	7-14
Community Acquired Pneumonia [§]	750 mg	5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10-14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7-14
Uncomplicated SSSI	500 mg	7-10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP) [¶]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP) [#]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg.	500 mg	60 ^{§§}

* Due to the designated pathogens.

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

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

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

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*.

P 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.

§§ the safety of Levofloxacin in adults for durations of therapy beyond 28 days has not been studied.

Dosage Adjustment in Adults with Renal Impairment

Administer Voloxal 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. No adjustment is necessary for patients with a creatinine clearance \geq 50 mL/min.

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

Table 2 shows how to adjust dose based on creatinine clearance.

Table 2: Dosage Adjustment 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 Ambulatory Dialysis (CAPD) or Chronic Peritoneal Dialysis

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

Voloxal Tablets should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets.

Voloxal Tablets can be administered without regard to food.

Adequate hydration of patients receiving Voloxal should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones.

Over Dosage

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

Presentation

Voloxal 500

Box of 7 tablets

Voloxal 750

Box of 7 tablets