LEVOFLOX Tablets (Levofloxacin)

Black Box Warning

Serious Adverse Reactions Including Tendinitis, Tendon Rupture, Peripheral Neuropathy, Central Nervous System Effects and Exacerbation Of Myasthenia Gravis

See full prescribing information for complete boxed warning.

• Fluoroquinolones, including Levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including:

- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects

Discontinue Levofloxacin immediately and avoid the use of fluoroquinolones, including Levofloxacin, in patients who experience any of these serious adverse reactions.

• Fluoroquinolones, including Levofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid Levofloxacin in patients with a known history of myasthenia gravis [see Warnings and Precautions].

• Because fluoroquinolones, including Levofloxacin, have been associated with serious adverse reactions, reserve Levofloxacin for use in patients who have no alternative treatment options for the following indications:

• Uncomplicated urinary tract infection
• Acute bacterial exacerbation of chronic bronchitis
• Acute bacterial sinusitis
• This drug may cause low blood sugar and mental health related side effects.

Composition

LEVOFLOX 250 Tablets

Each film-coated tablet contains:

Levofloxacin Hemihydrate, IP, equivalent to Levofloxacin ... 250 mg

Colours: Red Oxide of Iron and Titanium Dioxide

LEVOFLOX 500 Tablets

Each film-coated tablet contains:

Levofloxacin Hemihydrate, IP, equivalent to Levofloxacin ... 500 mg

Colours: Red Oxide of Iron and Titanium Dioxide

LEVOFLOX 750 Tablets

Each film-coated tablet contains

Levofloxacin Hemihydrate, IP, equivalent to Levofloxacin ... 750 mg

Colours: Titanium Dioxide

Dosage Form/S

Oral tablet

Pharmacology

Pharmacodynamics

Levofloxacin is the L-isomer 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 the inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Antimicrobial Activity

Levofloxacin has *in vitro* activity against Gram-negative and Gram-positive bacteria. Levofloxacin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in *Indications and Usage:*

Aerobic Bacteria

Gram Positive Bacteria

Enterococcus faecalis, Staphylococcus aureus (methicillin-susceptible isolates), *Staphylococcus epidermidis* (methicillin-susceptible isolates), *Staphylococcus saprophyticus, Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP][1]), *Streptococcus pyogenes*

[1] MDRSP (Multi-drug resistant *Streptococcus pneumoniae*) isolates are isolates resistant to two or more of the following antibiotics: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime; macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

Gram-Negative Bacteria

Enterobacter cloacae, Escherichia coli, Haemophilus influenza, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens.

Other Microorganisms

Chlamydophila pneumoniae, Mycoplasma pneumoniae,

The following *in vitro* data are available, but their clinical significance is unknown: Levofloxacin exhibits *in vitro* minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥90%) isolates of the following microorganisms; however, the safety and effectiveness of Levofloxacin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Aerobic Bacteria

Gram-Positive Bacteria

Staphylococcus haemolyticus, β-hemolytic Streptococcus (Group C/F), β-hemolytic Streptococcus (Group G), Streptococcus agalactiae, Streptococcus milleri, Viridans group streptococci, Bacillus anthracis

Gram-Negative Bacteria

Acinetobacter baumannii, Acinetobacter lwoffii, Bordetella pertussis, Citrobacter koseri, Citrobacter freundii, Enterobacter aerogenes, Enterobacter sakazakii, Klebsiella oxytoca, Morganella morganii, Pantoea agglomerans, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas fluorescens, Yersinia pestis

Anaerobic bacteria

Gram Positive Bacteria

Clostridium perfringens

Pharmacokinetics

The mean ± SD pharmacokinetic parameters of levofloxacin determined under single- and steady-state conditions following oral tablet. doses of levofloxacin are summarized in Table 1 below.

Table 1: Mean ± SD levofloxacin pharmacokinetic parameters

	C_{max}	T_{max}	AUC		$t_{1/2}$	
Regimen	**(mcg/mL)**	**(h)**	**(mcg·h/mL)**		**(h)**	
[3] Healthy males, 18 to 53 years of age						
[5] Healthy male and female subjects, 18 to 54 years of age						
[8] Healthy males, 22 to 75 years of age						
[9] Healthy females, 18 to 80 years of age						
[10] Young healthy male and female subjects, 18 to 36 years of age						
[11] Healthy elderly male and female subjects, 66 to 80 years of age						
* Absolute bioavailability: F=0.99 ± 0.08 from a 500-mg tablet and F=0.99 ± 0.06 from a 750-mg tablet						
ND=not determined.						
Single dose						
250 mg oral tablet[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9		7.3 ± 0.9	
500 mg oral tablet[3]*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8		6.3 ± 0.6	
750 mg oral tablet[5]*	9.3 ± 1.6	1.6 ± 0.8	101 ± 20		7.5 ± 0.9	
Multiple dose						
500 mg every 24 hours, oral tablet[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7		7.6 ± 1.6	
750 mg every 24 hours, oral tablet[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6		8.8 ± 1.5	
500 mg Oral Tablet Single Dose, Effects of Gender and Age						

Male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9		7.5 ± 2.1
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2		6.1 ± 0.8
Young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8		6.0 ± 0.9
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3		7.6 ± 2.0
500 mg Oral Single-Dose Tablet, Patients with Renal Impairment					
CLCR 50–80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8		9.1 ± 0.9
CLCR 20–49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6		27 ± 10
CLCR <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5		35 ± 5
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND		76 ± 42
Continuous ambulatory peritoneal dialysis (CAPD)	6.9 ± 2.3	1.4 ± 1.1	ND		51 ± 24

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1 to 2 hours after oral dosing. The absolute bioavailability of levofloxacin from a 500-mg tablet and a 750 mg tablet are both approximately 99%, demonstrating complete oral absorption of levofloxacin.

Levofloxacin pharmacokinetics is linear and predictable after single and multiple oral dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ± 1.4 mcg/mL after the 500 mg doses, and 8.6 ± 1.9 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500-mg dose of levofloxacin with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following intake of the tablet. Therefore, levofloxacin tablets can be administered without regard to food.

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

Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in the blister fluid of healthy subjects at approximately 3 hours after dosing. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5-fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 mcg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24–38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in the urine within 48 hours, whereas less than 4% of the dose was recovered in the feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

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

Special Populations

Pediatrics

Pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC0-24 and Cmax) to those observed in adult patients administered 500 mg of levofloxacin once every 24 hours. Levofloxacin tablets can be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths [*see Dosage and Administration]*

Indications

To reduce the development of drug-resistant bacteria and maintain the effectiveness of 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.

Levofloxacin 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 in this section.

Community-Acquired Pneumonia

Levofloxacin is indicated in adult patients for the treatment of community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-dru--resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila* or *Mycoplasma pneumoniae*.

Acute Bacterial Sinusitis

Levofloxacin is indicated in adult patients for the treatment of acute bacterial sinusitis (ABS) due to *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute Bacterial Exacerbation of Chronic Bronchitis

Levofloxacin is indicated in adult patients for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae* or *Moraxella catarrhalis*.

Skin and Soft Tissue Infections

Levofloxacin is indicated in adult patients for the treatment of uncomplicated skin and skin structure infections (mild to moderate), including abscesses, cellulitis, furuncles, impetigo, pyoderma and wound infections, due to methicillin-susceptible *Staphylococcus aureus* or *Streptococcus pyogenes*.

Levofloxacin is indicated in adult patients for the treatment of complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes* or *Proteus mirabilis*.

Complicated Urinary Tract Infections or Acute Pyelonephritis

Levofloxacin is indicated in adult patients for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Pseudomonas aeruginosa*.

Dosage and Administration

Dosage in Adult Patients with Normal Renal Function

The usual dose of levofloxacin tablets is 250 mg, 500 mg or 750 mg administered orally every 24 hours, as indicated by the infection and as described in Table 2. These recommendations apply to patients with creatinine clearance ≥ 50 mL/min. For patients with creatinine clearance <50 mL/min, adjustments to the dosing regimen are required

Table 2: Dosage in adult patients with normal renal function (CLCR ≥ 50 mL/min)

Type of Infection[1]	**Dosed Every 24 hours**	**Duration (days)**[2]
[1] Due to the designated pathogens [*see* **INDICATIONS**].		
[2] Sequential therapy (I.V. to oral) may be instituted at the discretion of the physician.		
[3] 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.*		
[4] Due to *Streptococcus pneumoniae* (excluding multi-drug-resistant strains [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*.		
[5] This regimen is indicated for complicated urinary tract infection (cUTI) due to *Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis*, and acute pyelonephritis (AP) due to *Escherichia coli*, including cases with concurrent bacteremia.		

[6] This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* and *Pseudomonas aeruginosa;* and for AP due to *Escherichia coli*.		
Community-acquired pneumonia[3]	500 mg	7–14
Community-acquired pneumonia[4]	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	750 mg	7–14
Uncomplicated skin and skin structure infections	500 mg	7–10
cUTI or Acute Pyelonephritis (AP)[5]	750 mg	5
cUTI or Acute Pyelonephritis (AP)[6]	250 mg	10

Dosage Adjustment in Adults with Renal Impairment

Administer levofloxacin with caution in the presence of renal impairment. 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 CLCR ≥50 mL/min.

In patients with impaired renal function (CLCR <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance. Table 4 shows how to adjust the dose, based on the CLCR.

Table 4: Dosage adjustment in adult patients with renal impairment (CLCR <50 mL/min)

Dosage in Normal Renal Function Every 24 hours	**CLCR 20 to 49 mL/min**	**CLCR 10 to 19 mL/min**	**Hemodialysis or CAPD**
750 mg every 24 hours	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 every 24 hours	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 every 24 hours	No dosage adjustment required	250 mg every 48 hours. If treating uncomplicated urinary tract infection, then no dosage adjustment is required	No information on dosing adjustment is available

Administration Instructions

Food and levofloxacin Tablets

Levofloxacin tablets can be administered without regard to food.

Hydration for Patients Receiving Levofloxacin Tablets

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

Contraindications

Levofloxacin is contraindicated in individuals with a known hypersensitivity to levofloxacin or another quinolone antibacterial.

Levofloxacin is contraindicated:

- in patients with hypersensitive to levofloxacin, to any other quinolones or to 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 and Precautions

Disabling and Potentially Irreversible Serious Adverse Reactions Including Tendinitis and Tendon Rupture, Peripheral Neuropathy, and Central Nervous System Effects

Fluoroquinolone, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting levofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions [please see warnings and precautions mentioned below].

Discontinue levofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolone, including levofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolone.

Tendinitis and Tendon Rupture

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. Tendinitis or tendon rupture can occur within hours or days of starting levofloxacin or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors 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 fluoroquinolone who do not have the above risk factors. Discontinue levofloxacin immediately 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. Avoid levofloxacin in patients who have a history of tendon disorders or tendon rupture.

Peripheral Neuropathy

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of 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 in some patients.

Discontinue levofloxacin 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. Avoid fluoroquinolones, including levofloxacin, in patients who have previously experienced peripheral neuropathy.

Central Nervous System Effects

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of central nervous system (CNS) effects, including convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri). Fluoroquinolones 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. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, discontinue levofloxacin and institute appropriate measures. As with other fluoroquinolones, levofloxacin should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse reactions including deaths and requirement for ventilator support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis.

Other Serious and Sometimes Fatal Adverse Reactions

Other serious and sometimes fatal adverse reactions, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolone, including levofloxacin. These events may be severe 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.

Discontinue levofloxacin immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures.

Hypersensitivity Reactions

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

Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

Clostridium difficile-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with the use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*.

CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte

management, protein supplementation, antibiotic treatment of *Clostridium difficile* and surgical evaluation should be instituted as clinically indicated.

Patients with G-6- Phosphate Dehydrogenase Deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Prolongation of the QT Interval

Some fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during post marketing surveillance in patients receiving fluoroquinolones, including levofloxacin. Levofloxacin should be administered with caution in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, patients with cardiac disease (e.g. heart failure, myocardial infarction, bradycardia) and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients and women may be more susceptible to drug-associated effects on the QT interval.

Blood Glucose Disturbances

As with other fluoroquinolone, disturbances of blood glucose, including symptomatic hyper-and hypoglycemia, have been reported with levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) 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 and appropriate therapy should be initiated immediately.

Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, “V” area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs.

Psychotic Reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behavior - sometimes after only a single dose of levofloxacin. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Vision Disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately

Development of Drug-Resistant Bacteria

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.

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Drug interactions

Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

Levofloxacin Tablets

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 2 hours before or 2 hours after oral levofloxacin administration.

Warfarin

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 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

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 Cmax and k_e were slightly lower while Tmax and t½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

Digoxin

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

Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the Cmax of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t½ 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.

Drugs known to prolong QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

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.

Renal impairment

Clearance of levofloxacin is substantially reduced and the plasma elimination half-life is substantially prolonged in adult patients with impaired renal function (CLCR <50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor CAPD is effective in the removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD (please refer to Dosage and Administration).

Hepatic impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin is not expected to be affected by hepatic impairment. Hence, no adjustment of dose is required since levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.

Pregnancy

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 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 below the age of six months have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species.

Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as levofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing levofloxacin to elderly patients especially those on corticosteroids.

Patients should be informed of this potential side effect and advised to discontinue levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur.

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis.

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 torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

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.

Undesirable Effects

The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class are as mentioned below;

- Disturbances in attention
- Disorientation
- Agitation
- Nervousness
- Memory impairment
- Serious disturbances in mental abilities called delirium.

Serious and Otherwise Important Adverse Reactions

The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of the labeling:

Disabling and Potentially Irreversible Serious Adverse Reactions [Please Refer Warnings and Precautions]

- Tendinitis and Tendon Rupture
- Hypersensitivity reactions
- Other serious and sometimes fatal reactions
- Hepatotoxicity
- Central nervous system effects
- *Clostridium difficile*-associated diarrhea
- Peripheral neuropathy
- Prolongation of the QT Interval
- Exacerbation of Myasthenia Gravis
- Musculoskeletal disorders in pediatric patients
- Blood glucose disturbances
- Photosensitivity/Phototoxicity
- Development of drug-resistant bacteria

Crystalluria and cylindruria have been reported with quinolones, including levofloxacin. Therefore, adequate hydration of patients should be maintained to prevent the formation of highly concentrated urine.Adverse reactions occurring in ≥1% of levofloxacin-treated patients and less common adverse reactions, occurring in 0.1 to <1% of levofloxacin-treated patients, are shown in Table 5 and Table

6, respectively. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation and dizziness.

Table 5: Common (≥1%) adverse reactions reported in clinical trials with levofloxacin

System/Organ Class	**Adverse Reaction**	**%**
		(N=7537)
[a] N=7274		
[b] N=3758 (women)		
Infections and Infestations	Moniliasis	1

Psychiatric Disorders	Insomnia[a]	4
Nervous System	Headache	6
Disorders	Dizziness	3
Respiratory, Thoracic and Mediastinal Disorders	Dyspnea	1
Gastrointestinal Disorders	Nausea	7
	Diarrhea	5
	Constipation	3
	Abdominal pain	2
	Vomiting	2
	Dyspepsia	2
Skin and Subcutaneous Tissue Disorders	Rash	2
	Pruritus	1
Reproductive System and Breast Disorders	Vaginitis	1[b]
General Disorders and Administration Site Conditions	Edema	1
	Injection site reaction	1
	Chest pain	1

Table 6: Less common (0.1 to 1%) adverse reactions reported in clinical trials with levofloxacin (N=7537)

System/Organ Class	**Adverse Reaction**
a N=7274	
Infections and Infestations	Genital moniliasis
Blood and Lymphatic System Disorders	Anemia

	Thrombocytopenia
	Granulocytopenia
Immune System Disorders	Allergic reaction
Metabolism and Nutrition Disorders	Hyperglycemia
	Hypoglycemia
	Hyperkalemia
Psychiatric Disorders	Anxiety
	Agitation
	Confusion
	Depression
	Hallucination
	Nightmarea
	Sleep disordera
	Anorexia
	Abnormal dreaminga
Nervous System Disorders	Tremor
	Convulsions
	Paresthesia
	Vertigo
	Hypertonia
	Hyperkinesias
	Abnormal gait
	Somnolencea
	Syncope
Respiratory, Thoracic and Mediastinal Disorders	Epistaxis
Cardiac Disorders	Cardiac arrest
	Palpitation
	Ventricular tachycardia
	Ventricular arrhythmia
Vascular Disorders	Phlebitis
Gastrointestinal Disorders	Gastritis
	Stomatitis
	Pancreatitis
	Esophagitis
	Gastroenteritis
	Glossitis
	Pseudomembraneous /Clostridium difficile colitis
Hepatobiliary Disorders	Abnormal hepatic function

	Increased hepatic enzymes
	Increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	Urticaria
Musculoskeletal and Connective Tissue Disorders	Arthralgia
	Tendinitis
	Myalgia
	Skeletal pain
Renal and Urinary Disorders	Abnormal renal function
	Acute renal failure

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with quinolones, including Levofloxacin. The relationship of the drugs to these events is not presently established.

Post-marketing Experience

Table 7 lists adverse reactions that have been identified during the post-approval use of levofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 7: Post marketing reports of adverse drug reactions

System/Organ Class	**Adverse Reaction**	
Blood and Lymphatic	Pancytopenia	
System Disorders	Aplastic anemia	
	Leukopenia	
	Hemolytic anemia	
	Eosinophilia	
Immune System Disorders	Hypersensitivity reactions, sometimes fatal, including	
	anaphylactic/anaphylactoid reactions	
	Anaphylactic shock	
	Angioneurotic edema	
	Serum sickness	

Psychiatric Disorders	Psychosis	
	Paranoia	
	Isolated reports of suicide attempt and suicidal ideation	
	Insomnia	
Nervous System Disorders	Exacerbation of myasthenia gravis Anosmia	
	Headache	
	Dizziness	
	Ageusia	
	Parosmia	
	Dysgeusia	
	Peripheral neuropathy	
	Isolated reports of encephalopathy	
	Abnormal electroencephalogram (EEG)	
	Dysphonia pseudotumor cerebri	
Eye Disorders	Uveitis, Vision disturbance, including diplopia	
	Visual acuity reduced	
	Vision blurred	
	Scotoma	
Ear and Labyrinth Disorders	Hypoacusis	
	Tinnitus	
Cardiac Disorders	Isolated reports of *torsades de pointes*	
	Electrocardiogram QT prolonged	
	Tachycardia	
Vascular Disorders	Vasodilatation	
Respiratory, Thoracic and Mediastinal Disorders	Isolated reports of allergic pneumonitis	
	Bronchospasm	
Hepatobiliary Disorders	severe liver injury (including fatal acute liver failure, primarily in patients with severe underlying diseases)	
	Hepatitis	
	Jaundice	
	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	
	Blood bilirubin increased	

Gastro-intestinal Disorders	Diarrhea	
	Vomiting	
	Nausea	
	Abdominal pain	
	Dyspepsia	
	Flatulence	
	Constipation	
	Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis	
	Pancreatitis	
Skin and Subcutaneous Tissue Disorders	Rash	
	Pruritus	
	Urticaria	
	hyperhidrosis	
	Bullous eruptions, including Stevens-Johnson syndrome	
	Toxic epidermal necrolysis Acute Generalized Exanthematous Pustulosis (AGEP) fixed drug eruptions	
	Erythema multiforme	
	Photosensitivity/photoxicity reaction Leukocytoclastic vasculitis	
Musculoskeletal and Connective Tissue Disorders	Tendon rupture, tendon disorders (tendinitis, e.g., Achilles tendon)	
	Muscle injury, including rupture	
	Rhabdomyolysis	
	Arthralgia	
	Myalgia	
	Muscular weakness which may be of special importance in patients with myasthenia gravis	
Renal and Urinary Disorders	Renal failure acute (e.g., due to Interstitial nephritis)	
	Blood creatinine increased	
General Disorders and Administration Site Conditions	Multi-organ failure	
	Pyrexia	
	Asthenia	
	Pain (including pain in back, chest, and extremities)	
Investigations	Prothrombin time prolonged	
	International normalized ratio prolonged	

	Muscle enzymes increased

Effects on Ability to Drive and Use Machines

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, and visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

If you experience any side-effects, talk to your doctor or pharmacist or write to drugsafety@cipla.com. You can also report side effects directly via the national pharmacovigilance program of India by calling on 18002677779 (Cipla Number) or you can report to PvPI on 1800 180 3024.

By reporting side-effects, you can help provide more information on the safety of this product.

Overdosage

In the event of an acute over dosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by haemodialysis or peritoneal dialysis. Levofloxacin exhibits a low potential for acute toxicity.

Storage and Handling Instructions

LEVOFLOX Tablets: Protect from light and moisture.

Packaging Information

LEVOFLOX 250/500 Tablets: Blister pack of 10 tablets

LEVOFLOX 750 Tablets: Blister pack of 5 tablets

Last Updated: April 2019

Last Reviewed: April 2019