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PRODUCT MONOGRAPH

[Pr]LEVAQUIN*

levofloxacin

Tablets 250 mg, 500 mg and 750 mg

and

For injection 25 mg/mL

Injection 5 mg/mL in 5% dextrose

Antibacterial Agent

Janssen-Ortho Inc.
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DATE OF PREPARATION:
November 5, 1997

DATE OF REVISION:
July 12, 2006

Control No.: 105554

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ACTION AND CLINICAL PHARMACOLOGY

Action

LEVAQUIN levofloxacin is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration.

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antibacterial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other quinolone antibacterials involves inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Topoisomerases are essential in controlling the topological state of DNA, and are vital for DNA replication, transcription, repair and recombination.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from other classes of antimicrobial agents, such as β-lactam antibiotics, aminoglycosides, and macrolides. Therefore, microorganisms resistant to these latter classes of antimicrobial agents may be susceptible to fluoroquinolones. For example, β-lactamase production and alterations in penicillin-binding proteins have no effect on levofloxacin activity. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to other classes of antimicrobial agents.

Clinical Pharmacology

Pharmacokinetics

Absorption

Oral

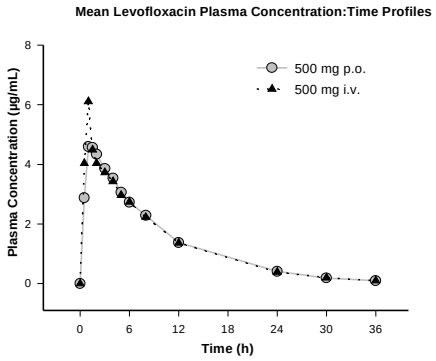
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1 to 2 hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin is approximately 99% in both cases, demonstrating complete oral absorption of levofloxacin. Levofloxacin pharmacokinetics are 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 peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 µg/mL and 0.5 µg/mL after the 500 mg doses, and 8.6 µg/mL and 1.1 µg/mL after the 750 mg doses, respectively.

There was no clinically significant effect of food on the extent of absorption of levofloxacin. Oral administration with food slightly prolongs the time to peak concentration by approximately 1 hour, and slightly decreases the peak concentration by approximately 14%. Therefore, levofloxacin can be administered without regard to food.

I.V.

Following a single intravenous dose of levofloxacin to healthy volunteers, the mean peak plasma concentration attained was 6.2 µg/mL after a 500 mg dose infused over 60 minutes, and 7.99 µg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin pharmacokinetics are linear and predictable after single and multiple i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosing regimen. The peak and trough plasma concentrations attained following multiple once-daily i.v. regimens were approximately 6.4 µg/mL and 0.6 µg/mL after the 500 mg doses, and 7.92 µg/mL and 0.85 µg/mL after the 750 mg doses, respectively.

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 (see following figure).



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 (11.7 µg/g for a 750 mg dose) and in blister fluid (4.33 µg/g for a 500 mg dose) at approximately 3-4 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2. The blister fluid to plasma AUC ratio is approximately 1, following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin to healthy subjects, respectively. Levofloxacin also penetrates 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 µg/g over a 24-hour period after a single 500 mg oral dose.

Levofloxacin is 24 to 38% bound to serum proteins across all species studied. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine, and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans, and is primarily excreted as unchanged drug (87%) in the urine within 48 hours.

Excretion

The major route of elimination of levofloxacin in humans is 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 or intravenously.

Summary of Pharmacokinetics

The mean (± SD) pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral (p.o.) or intravenous (i.v.) doses of levofloxacin are summarized in the following table.

Summary of Pharmacokinetic Parameters (mean ± SD)

Regimen	N	C_{max} (µg/mL)	T_{max} (h)	AUC[j] (µg•h/mL)	CL/F (mL/min)	Vd/F (L)	$t_{1/2}$ (h)	Cl_r (mL/min)
Single dose								
250 mg p.o.[a]	15	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg p.o.[a]*	23	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg i.v.[a]	23	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg p.o.[cc]	10	7.1 ± 1.4	1.9 ± 0.7	82.2 ± 14.3	157 ± 28	90 ± 14	7.7 ± 1.3	118 ± 28
750 mg i.v.[c]	4	7.99 ± 1.2[b]	ND	74.4 ± 8.0	170 ± 19	97.0 ± 14.8	7.5 ± 1.9	ND
Multiple dose								
500 mg q24h p.o.[a]	10	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7[x]	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v.[a]	10	6.4 ± 0.8	ND	54.6 ± 11.1[x]	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg q24h i.v. patients with bacterial infections[d]	272	8.7 ± 4.0[i]	ND	72.5 ± 51.2[i,x]	154 ± 72	111 ± 58	ND	ND
750 mg q24h p.o.[cc]	10	8.6 ±1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg q24h i.v.[c]	4	7.92 ± 0.91[b]	ND	72.5 ± 0.8[x]	172 ± 2	111 ± 12	8.1 ± 2.1	ND
500 mg p.o. single dose, effects of gender and age:								
male[e]	12	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
female[f]	12	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
young[g]	12	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
elderly[h]	12	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg p.o. single dose, patients with renal insufficiency:								
Cl_{Cr} 50-80 mL/min	3	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
Cl_{Cr} 20-49 mL/min	8	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
Cl_{Cr} < 20 mL/min	6	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
hemodialysis	4	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	4	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND
750 mg i.v. single dose and multiple dose, patients with renal insufficiency:								
Single dose - Cl_{Cr} 50-80 mL/min[k]	8	13.3 ± 3.6	ND	128 ± 37	104 ± 25	62.7 ± 15.1	7.5 ± 1.5	ND
Multiple q24h dose - Cl_{Cr} 50-80 mL/min[k]	8	14.3 ± 3.2	ND	145 ± 36	103 ± 20	64.2 ± 16.9	7.8 ± 2.0	ND

[a] healthy males 18-53 years of age;
[b] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose;
[c] healthy male subjects 32-46 years of age;
[cc] healthy male subjects 19-51 years of age;
[d] including 500 mg q48h for 8 patients with moderate renal impairment (Cl_{Cr}20-50 mL/min) and infections of the respiratory tract or skin;
[e] healthy males 22-75 years of age;
[f] healthy females 18-80 years of age;
[g] young healthy male and female subjects 18-36 years of age;
[h] healthy elderly male and female subjects 66-80 years of age;
[i] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modelling;
[j] AUC for 0-∞ reported, unless otherwise specified;
[k] male and female subjects 34-54 years of age;
[x] $AUC_{0\text{-}24\ h}$;
* 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

Factors Influencing the Pharmacokinetics

Special Populations

Elderly

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

Pediatric

The pharmacokinetics of levofloxacin in pediatric patients have not been studied.

Gender

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when the differences in creatinine clearance are taken into consideration. Dose adjustment based on gender alone is not necessary.

Renal Insufficiency

Pharmacokinetic parameters of levofloxacin following oral or intravenous doses of levofloxacin in patients with impaired renal function (creatinine clearance ≤ 80 mL/min) are presented in *Summary of Pharmacokinetics*. Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in this patient population. Dosage adjustment may be required in such patients to avoid accumulation.

A dosage reduction is being recommended depending on the levels of renal insufficiency. Dosing recommendations are based on pharmacokinetic modeling of data collected from a clinical safety and pharmacokinetic study in renally impaired patients treated with a single 500 mg oral dose of levofloxacin (see **PRECAUTIONS**: **Renal,** and **DOSAGE AND ADMINISTRATION**: Patients with Impaired Renal Function).

Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating supplemental doses of levofloxacin are not required following hemodialysis or CAPD.

Hepatic Insufficiency

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial Infection

The pharmacokinetics of levofloxacin in patients with community-acquired bacterial infections are comparable to those observed in healthy subjects.

Studies Measuring Effects on QT and Corrected QT (QTc) Intervals

Two studies have been conducted to assess specifically the effect of levofloxacin on QT and corrected QT (QTc) intervals in healthy adult volunteers. In a dose escalation study (n=48) where the effect on average QTc, after single doses of 500, 1000, and 1500 mg of levofloxacin, were measured between the baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) and the average post-dose QTc interval (calculated from measurements taken every half hour for two hours and at 4, 8, 12 and 24 hours after treatment), an effect on the average QTc (Bazett) was –1.84, 1.55 and 6.40 msec, respectively. In a study which compared the effect of 3 antimicrobials (n=48) where the difference was measured between the baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) and the average post-dose QTc interval (calculated from measurements taken every half hour for four hours and at 8, 12 and 24 hours after treatment), an effect on the average QTc was an increase of 3.58 msec after the 1000 mg dose of levofloxacin. The mean increase compared to baseline of QTc at C_{max} in these two trials was 7.82 msec and 5.32 msec after a single 1000 mg dose. In these trials, no effect on QT intervals compared to placebo was evident at any of the doses studied. The clinical relevance of the results of these studies is not known.

INDICATIONS AND CLINICAL USE

LEVAQUIN levofloxacin Tablets and Injection are indicated for the treatment of adults with bacterial infections caused by susceptible strains of the designated microorganisms in the infections listed below.

Note: Since i.v. and oral formulations are interchangeable, i.v. administration is recommended only when it offers a route of administration advantageous to the patient (e.g. patient cannot tolerate oral dosage form).

Upper Respiratory Tract

Acute sinusitis (mild to moderate) due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella (Branhamella) catarrhalis*.

Lower Respiratory Tract

Acute bacterial exacerbations of chronic bronchitis (mild to moderate) due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella (Branhamella) catarrhalis*.

Community-acquired pneumonia (mild, moderate and severe infections) due to *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Haemophilus influenzae*, *Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella (Branhamella) catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae* (see **DOSAGE AND ADMINISTRATION**, and **PHARMACOLOGY: Clinical Studies**).

Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae* or *Streptococcus pneumoniae.* Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

Skin and Skin Structure

Uncomplicated skin and skin structure infections (mild to moderate) due to *Staphylococcus aureus* or *Streptococcus pyogenes*.

Complicated skin and skin structure infections (mild to moderate), excluding burns, due to *Enterococcus faecalis,* methicillin-sensitive *Staphylococcus aureus, Streptococcus pyogenes, Proteus mirabilis,* or *Streptococcus agalactiae.*

Urinary Tract

Complicated urinary tract infections (mild to moderate) due to *Enterococcus (Streptococcus) faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, or *Pseudomonas aeruginosa.*

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae,* or *Staphylococcus saprophyticus*.

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli.*

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis,* or *Staphylococcus epidermidis*.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing the infection, and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before the results of these tests are known; once results become available, appropriate therapy should be continued.

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 reveal not only the therapeutic effect of the antimicrobial agent, but also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

LEVAQUIN levofloxacin Tablets and Injection are contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product. Levofloxacin is also contraindicated in persons with a history of tendonitis or tendon rupture associated with the use of any member of the quinolone group of antimicrobial agents.

WARNINGS

THE SAFETY AND EFFICACY OF LEVAQUIN LEVOFLOXACIN TABLETS AND INJECTION IN CHILDREN, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING MOTHERS HAVE NOT BEEN ESTABLISHED (see **PRECAUTIONS: Pediatric Use, Pregnancy,** and **Nursing Mothers**).

The oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis in immature rats and dogs. Other quinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species. Consequently, levofloxacin should not be used in pre-pubertal patients (see **TOXICOLOGY**).

Sexually Transmitted Diseases

Levofloxacin is not indicated for the treatment of syphilis or gonorrhea. Levofloxacin is not effective in the treatment of syphilis. Antimicrobial agents used in high doses for short periods of time to treat gonorrhea may mask or delay the symptoms of incubating syphilis. All patients with gonorrhea should have a serologic test for syphilis at the time of diagnosis. Patients treated with antimicrobial agents with limited or no activity against *Treponema pallidum* should have a follow-up serologic test for syphilis after 3 months.

Hypersensitivity Reactions

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 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 (see **ADVERSE REACTIONS**).

Serious and sometimes fatal events, some due to hypersensitivity and some due to uncertain etiology, have rarely been reported in patients receiving therapy with quinolones, 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. The administration of levofloxacin should be discontinued immediately, at the first appearance of a skin rash or any other sign of hypersensitivity, and supportive measures instituted (see **ADVERSE REACTIONS**).

CNS and Psychiatric Effects

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones including levofloxacin, may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, dizziness, confusion and 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, the drug should be discontinued and appropriate measures instituted. As with all 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. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. alcohol abuse, certain drug therapies such as NSAIDs and theophylline, renal dysfunction). Levofloxacin should be used with caution in patients with unstable psychiatric illness (see **PRECAUTIONS: Drug Interactions,** and **ADVERSE REACTIONS**).

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.

Gastrointestinal Effects

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 agents alters the normal flora of the colon, and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a 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**).

Musculoskeletal 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 (see **CONTRAINDICATIONS**).

PRECAUTIONS

Although levofloxacin is soluble, adequate hydration of patients receiving LEVAQUIN levofloxacin should be maintained to prevent the formation of a highly concentrated urine. Crystalluria has been observed rarely in patients receiving other quinolones, when associated with high doses and an alkaline urine. Although crystalluria was not observed in clinical trials with levofloxacin, patients are encouraged to remain adequately hydrated.

As with any antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy (see **WARNINGS,** and **ADVERSE REACTIONS**).

I.V. Administration

Because rapid or bolus intravenous injection may result in hypotension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 MINUTES FOR A 500 MG DOSE, AND 90 MINUTES FOR A 750 MG DOSE (see **DOSAGE AND ADMINISTRATION**).

Renal

Safety and efficacy of levofloxacin in patients with impaired renal function (creatinine clearance $\leq$ 80 mL/min) have not been studied. Since levofloxacin 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. The potential effects of levofloxacin associated with possible increased serum/tissue levels in renal impaired patients, such as effect on QTc interval, have not been studied. Adjustment of the dosage regimen may be necessary to avoid the accumulation of levofloxacin due to decreased clearance. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy, since elimination of levofloxacin may be reduced. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Administer levofloxacin with caution in the presence of renal insufficiency (See **DOSAGE AND ADMINISTRATION**: Patients with Impaired Renal Function, and **ACTION AND CLINICAL PHARMACOLOGY**: *Renal Insufficiency*).

Phototoxicity

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 phototoxicity (e.g. skin eruption) occurs.

Pregnancy

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 (see **WARNINGS** and **TOXICOLOGY**).

Nursing Mothers

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin can 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 (see **WARNINGS,** and **TOXICOLOGY**).

Pediatric Use

Safety and effectiveness in children and adolescents (below the age of 18 years) have not been established. Levofloxacin, like other quinolones, causes arthropathy and osteochondrosis in juvenile animals of several species (see **WARNINGS,** and **TOXICOLOGY**).

Geriatric Use

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. It may also be useful to monitor renal function.

Disturbances of Blood Glucose

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 hypoglycemic 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, discontinue levofloxacin immediately and initiate appropriate therapy (see **Drug Interactions**, and **ADVERSE REACTIONS**).

QT Prolongation

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. During post-marketing surveillance, very rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including macrolide antibiotics, antipsychotics, tricyclic antidepressants, Class IA (e.g. quinidine,

procainamide) or Class III (e.g. amiodarone, sotalol) antiarrhythmic agents, and cisapride. In addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, cardiomyopathy, patients with myocardial ischemia, and patients with congenital prolongation of the QT interval should be avoided (see **ACTION AND CLINICAL PHARMACOLOGY**: Studies Measuring Effects on QT and Corrected QT (QTc) Intervals).

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multi-Vitamins

LEVAQUIN levofloxacin Tablets

Due to the chelation of levofloxacin by multivalent cations, concurrent administration of LEVAQUIN Tablets with antacids containing calcium, magnesium, or aluminum, as well as sucralfate, metal cations such as iron, multi-vitamin preparations with zinc, or any products containing any of these components may 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 levofloxacin tablet administration.

LEVAQUIN levofloxacin Injection

There are no data concerning an interaction of intravenous quinolones with oral antacids, sucralfate, multi-vitamins, or metal cations. Levofloxacin should not be co-administered with any solution containing multivalent cations (e.g. magnesium) through the same intravenous line (see **PHARMACEUTICAL INFORMATION: Preparation of LEVAQUIN levofloxacin Parenteral Products for 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, 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 theophylline dosage adjustments made if appropriate, when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline level (see **WARNINGS**).

Warfarin

Certain quinolones, including levofloxacin, may enhance the effects of oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time, International Normalized Ratio (INR), or other suitable coagulation tests should be monitored closely, especially in the elderly patients.

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 C_{max} and k_e were slightly lower, while T_{max} and $t_{½}$ 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 rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and Cl_r were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although the 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: CNS and Psychiatric Effects**, and **PHARMACOLOGY: Animal Pharmacology**).

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 these agents, including levofloxacin, are co-administered.

Zidovudine

Levofloxacin absorption and disposition in HIV-infected subjects, with or without concomitant zidovudine treatment, were similar. Therefore, no dosage adjustment for levofloxacin appears to be required when co-administered with zidovudine. The effect of levofloxacin on zidovudine pharmacokinetics has not been studied.

Monitoring and Laboratory Tests

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.

ADVERSE REACTIONS

In North American Phase 3 clinical trials involving 5912 subjects, the incidence of treatment-emergent adverse events in patients treated with LEVAQUIN levofloxacin Tablets and Injection was comparable to controls. The majority of adverse events were considered to be mild to moderate, with 6.7% of patients considered to have severe adverse events. Among patients receiving multiple-dose therapy, 4.4% discontinued therapy with levofloxacin due to adverse experiences. The incidence of drug-related adverse reactions was 6.3%.

In Phase 3 clinical trials, the adverse events in the following table were characterized as likely related to drug therapy for patients receiving multiple doses of levofloxacin.

Body System	Adverse Events Considered Likely to Be Drug-Related (n=5912)	
	Event	Percentage of patients with ADR
Application Site Disorder	injection site pain injection site reaction injection site inflammation	0.2 0.2 0.1
Body as a Whole - General Disorders	allergic reaction condition aggravated	0.1 0.1
Gastrointestinal System	nausea diarrhea abdominal pain flatulence dyspepsia vomiting constipation Mouth Dry	1.2 1.0 0.4 0.3 0.2 0.2 0.1 0.1
Genital/Reproductive System	vaginitis genital moniliasis genital pruritus	0.6 0.2 0.1
Nervous System	insomnia dizziness headache nervousness agitation anorexia tremor	0.4 0.3 0.2 0.1 0.1 0.1 0.1

Body System	Adverse Events Considered Likely to Be Drug-Related (n=5912)	
	Event	Percentage of patients with ADR
Respiratory System Disorder	dyspnoea	0.1
Resistance Mechanism Disorders	moniliasis fungal infection	0.2 0.1
Special Senses	taste perversion	0.2
Skin/Hypersensitivity	rash pruritus urticaria rash erythematous rash maculo-papular	0.3 0.3 0.1 0.1 0.1

In clinical trials, the most frequently reported adverse events occurring in > 3% of the study population, regardless of drug relationship, were:

nausea 6.9%
headache 6.1%
diarrhea 5.5 %
insomnia 4.9%
constipation 3.4%

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship:

abdominal pain 2.6%
dizziness 2.5%
vomiting 2.4%
dyspepsia 2.3%
vaginitis 1.6%
rash 1.5%
pain 1.5%
dyspnea 1.4%
chest pain 1.3%
fatigue 1.3%
back pain 1.2%
flatulence 1.2%
pruritus 1.2%
rhinitis 1.2%
sinusitis 1.2%
anxiety 1.1%
pharyngitis 1.1%

In clinical trials, the following events of potential medical importance occurred at a rate of 0.1 to 0.9%, regardless of drug relationship:

Application Site Disorder: injection site inflammation, injection site pain, injection site reaction

Body as a Whole - General Disorders:	ascites, allergic reaction, asthenia, condition aggravated, drug level increase, edema, enlarged abdomen, fever, hot flushes, influenza-like symptoms, leg pain, malaise, rigors, substernal chest pain, syncope, multiple organ failure, changed temperature sensation, withdrawal syndrome
Cardiovascular Disorders - General:	cardiac failure, circulatory failure (< 0.1%), hypertension, hypertension aggravated, hypotension, postural hypotension
Central and Peripheral Nervous System Disorders:	abnormal gait, ataxia, convulsions (seizures), dysphonia, dystonia, encephalopathy, hyperesthesia, hyperkinesia, hypertonia, hypoesthesia, intracranial hypertension, involuntary muscle contractions, leg cramps, migraine, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo
Gastrointestinal System Disorders:	dry mouth, dysphagia, esophagitis, gastritis, gastroenteritis, gastroesophageal reflux, G.I. hemorrhage, glossititis, hemorrhoids, intestinal obstruction, pancreatitis, tongue edema, melena, stomatitis, stomatitis ulcerative, tooth disorder
Hearing and Vestibular Disorders:	ear ache, tinnitus
Heart Rate and Rhythm Disorders:	arrhythmia, arrhythmia ventricular, atrial fibrillation, bradycardia, cardiac arrest, heart block, palpitation, supraventricular tachycardia, ventricular fibrillation, ventricular tachycardia, tachycardia
Liver and Biliary System Disorders:	abnormal hepatic function, cholecystitis, cholelithiasis, elevated bilirubin, hepatic failure, increased hepatic enzymes, jaundice
Metabolic and Nutritional Disorders:	BUN increased, dehydration, electrolyte abnormality, fluid overload, gout, hyperglycemia, hyperkalemia, hypernatremia, hypoglycemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, nonprotein nitrogen increase, thirst, weight decrease
Musculo-Skeletal System Disorders:	arthralgia, arthritis, arthrosis, myalgia, osteomyelitis, pathological fracture, skeletal pain, synovitis, tendinitis, tendon disorder
Myo-, Endo-, Pericardial and Valve Disorders:	angina pectoris, endocarditis, myocardial infarction
Neoplasms:	carcinoma, hepatic neoplasm, 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, confusion, depression, hallucination, impotence, nervousness, paranoia, sleep disorder, somnolence
Red Blood Cell Disorders:	anemia
Reproductive Disorders:	dysmenorrhea, leukorrhea, penis disorder, sexual function abnormal
Resistance Mechanism Disorders:	abscess, bacterial infection, fungal infection, herpes simplex, otitis media, sepsis, viral infection
Respiratory System Disorders:	airways obstruction, aspiration, asthma, bronchitis, bronchospasm, chronic obstruct airway disease, coughing, epistaxis, hemoptysis, hypoxia, laryngitis, pleural effusion, pleurisy, pneumonia, pneumonitis, pneumothorax, pulmonary collapse, pulmonary edema, respiratory depression, 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, dysuria, face edema, haematuria, renal calculus, oliguria, urine abnormal, urinary incontinence, urinary retention, urinary tract infection
Vascular (Extracardiac) Disorders:	cerebrovascular disorder, flushing, gangrene, phlebitis, purpura, thrombophlebitis (deep)
Vision Disorders:	abnormal vision, eye abnormality, eye pain, conjunctivitis
White Cell and RES Disorders:	agranulocytosis, granulocytopenia, leukocytosis, lymphadenopathy, WBC abnormal (not otherwise specified)

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.

Laboratory abnormalities seen in > 2% of patients receiving multiple doses of levofloxacin:

decreased glucose 2.3%

decreased lymphocytes 2.2%

It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Post-marketing Adverse Reactions

Additional serious adverse events reported with levofloxacin, regardless of drug relationship include:

acute renal insufficiency or failure, ageusia, agranulocytosis, allergic pneumonitis, amnesia, anaphylactic shock, anaphylactoid reaction, angioedema, anosmia, aplastic anemia, apnea, arthralgia, DIC, dysgeusia, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, fever, glomerulonephritis, decreased hearing, hemolytic anemia, hepatic necrosis, hepatitis, increased International Normalized Ratio (INR)/prothrombin time, interstitial nephritis, interstitial pneumonia, laryngeal edema, liver failure, increased muscle enzymes (CPK), multi-system organ failure, muscle injury including rupture, myalgia, leukopenia, myositis, nephrosis, pancytopenia, rash, rhabdomyolysis, Stevens-Johnson syndrome, serum sickness, tendon rupture, thrombocytopenia including thrombotic thrombocytopenic purpura, toxic epidermal necrolysis, torsades de pointes, vasculitis, vasodilation, abnormal vision (blurred vision, diplopia, decreased vision, scotomata).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In the event of an acute overdosage, the stomach should be emptied. The patient should be observed, including ECG monitoring (see **ACTION AND CLINICAL PHARMACOLOGY**, Studies Measuring Effects on QT and Corrected QT (QTc) Intervals), and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION

Dosage

Tablets and Injection

The dosage of LEVAQUIN levofloxacin Tablets and Injection for patients with normal renal function (i.e. Cl_{Cr} > 80 mL/min) is described in the following dosing chart. For patients with altered renal function (i.e. Cl_{Cr} $\leq$ 80 mL/min), see the Patients with Impaired Renal Function subsection. The 250 mg and 500 mg doses of

LEVAQUIN Injection should be administered by slow infusion over 60 minutes every 24 hours while the 750 mg dose is administered by slow infusion over 90 minutes every 24 hours.

Patients with Normal Renal Function

Infection*	Dose	Freq.	Duration**
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days
	750 mg	q24h	5 days
Comm.- Acquired Pneumonia	500 mg	q24h	7-14 days (10-14 days for severe infections)
	750 mg***	q24h	5 days
Sinusitis	500 mg	q24h	10-14 days
Nosocomial Pneumonia	750 mg	q24h	7-14 days
Uncomplicated SSSI	500 mg	q24h	7-10 days
Complicated SSSI	750 mg	q24h	7-14 days
Chronic Bacterial Prostatitis	500 mg	q24h	28 days
Complicated UTI	250 mg	q24h	10 days
Acute Pyelonephritis	250 mg	q24h	10 days
Uncomplicated UTI	250 mg	q24h	3 days

* DUE TO THE DESIGNATED PATHOGENS (see **INDICATIONS AND CLINICAL USE**).
** TOTAL THERAPY DURATION. When appropriate, patients may be converted from LEVAQUIN Injection to an equivalent dose of LEVAQUIN Tablets.
*** Efficacy of this alternative regimen has only been documented for infections caused by penicillin-susceptible *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila*.

Patients with Impaired Renal Function

On the basis of the altered levofloxacin disposition pharmacokinetics in subjects with impaired renal function, dose adjustment is recommended for patients with impaired renal function as given below (see **ACTION AND CLINICAL PHARMACOLOGY**: *Renal Insufficiency*, and **PRECAUTIONS**: **Renal**).

Dosing recommendations for renally impaired patients are based on data collected from a clinical safety and pharmacokinetic study in renally impaired patients treated with a single 500 mg oral dose of levofloxacin. There is no clinical experience available in this patient population for the 250 mg dose or 750 mg dose. Pharmacokinetic modeling was used to determine a recommended dosing regimen which would provide equivalent drug exposures for which clinical efficacy has been demonstrated. The potential effects of levofloxacin associated with possible increased serum/tissue levels in renal impaired patients, such as effect on QTc interval, have not been studied.

Renal Status	Initial Dose	Subsequent Dose
Acute Sinusitis / Acute Bacterial Exacerbation of Chronic Bronchitis / Community Acquired Pneumonia / Uncomplicated SSSI / Chronic Bacterial Prostatitis		
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 UTI / Acute Pyelonephritis		
$Cl_{Cr} \geq$ 20 mL/min	No dosage adjustment required	
Cl_{Cr} from 10 to 19 mL/min	250 mg	250 mg q48h
Complicated SSSI / Nosocomial Pneumonia / Community Acquired Pneumonia/Acute Bacterial Exacerbation of Chronic Bronchitis		
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
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.

Men: Creatinine Clearance (mL/min)

$$= \frac{\text{Weight (kg) x (140 - age)}}{\text{serum creatinine (µmol/L)}} \times 1.2$$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

Administration

Tablets

Levofloxacin can be administered without regard to food. Doses should be administered at least 2 hours before or 2 hours after antacids containing calcium, magnesium, aluminum, sucralfate, metal cations such as iron, multi-vitamin preparations with zinc, or products containing any of these components.

Injection

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin injection should be infused intravenously, slowly over a period of not less than 60 minutes for a 250 mg or a 500 mg dose, and not less than 90 minutes for a 750 mg dose. LEVAQUIN Injection should only be administered by

intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration (see **PRECAUTIONS**).

Single-use vials require dilution prior to administration. The concentration of the resulting diluted solution should be 5 mg/mL prior to administration (see **PHARMACEUTICAL INFORMATION: Preparation of LEVAQUIN levofloxacin Parenteral Products for Administration**).

This parenteral drug product should be inspected visually for particulate matter prior to administration. Units containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic techniques must be used in preparation of the final parenteral solution. **Since the vials are for single use only, any unused portion remaining in the vial should be discarded. When used for split dosing, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use** (see **PHARMACEUTICAL INFORMATION: Stability of LEVAQUIN Injection Following Dilution**).

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

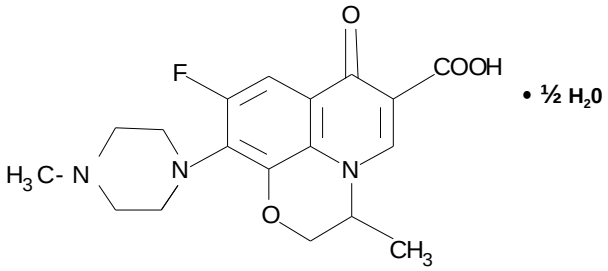
PHARMACEUTICAL INFORMATION

Drug Substance

Proper or Common Name: levofloxacin

Chemical Name: (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate

Chemical Structure:



Molecular Formula: $C_{18}H_{20}FN_3O_4 \bullet ½ H_2O$

Molecular Weight: 370.38

Description:

Levofloxacin is a light yellowish white to yellow-white crystal or crystalline powder with a melting point of 226-227°C. The pK_a values for levofloxacin are 5.33 and 8.07 for pK_{a1} and pK_{a2}, respectively. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that, from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble to freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL), and is considered *freely soluble* in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9. Levofloxacin is considered *freely soluble to soluble* at the pH range of 6.7 to 7.7, beyond which the solubility begins to increase again.

Levofloxacin has the potential to form stable co-ordination compounds with many metal ions. This in vitro chelation potential has the following formation order: $Al^{+3} > Cu^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2}$.

Composition

LEVAQUIN Tablets

LEVAQUIN levofloxacin Tablets are available as film-coated tablets (expressed in the anhydrous form) and contain the following inactive ingredients:

250 mg: hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red iron oxide.

500 mg: hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red and yellow iron oxides.

750 mg: hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, and polysorbate 80.

LEVAQUIN Injection

LEVAQUIN Injection in Single-Use Vials (25 mg/mL)

LEVAQUIN Injection in Single-Use Vials is a sterile, preservative-free solution of levofloxacin, at 25 mg/mL in Water for Injection, with a pH ranging from 3.8 to 5.8. The solution may contain hydrochloric acid, NF and/or sodium hydroxide, and NF for pH adjustment. The appearance of LEVAQUIN Injection may range from a clear yellow to greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN Injection in Premix Flexible Containers (5 mg/mL)

LEVAQUIN Injection in Premix flexible containers is a sterile, preservative-free, non-pyrogenic premixed solution that contains levofloxacin, at 5 mg/mL in 5% dextrose (D_5W). The solution has a pH ranging from 3.8 to 5.8. Solutions of hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH.

The flexible container is fabricated from a specially formulated non-plasticized, thermoplastic copolyester (CR3). The amount of water that can permeate from the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic containers.

Stability and Storage Recommendations

Tablets

LEVAQUIN Tablets should be stored at controlled room temperature (15-30°C) in well-closed containers.

Injection

When stored under recommended conditions, LEVAQUIN Injection, as supplied in vials and flexible containers, is stable through the expiration date printed on the label.

LEVAQUIN Injection in Single Use Vials should be stored at 2-30°C and be protected from light.

LEVAQUIN Injection PREMIX in flexible containers should be stored at 2-25°C; however, brief exposure up to 40°C does not adversely affect the product. Avoid excessive heat and protect from freezing and light. Store with protective overwrap.

Preparation of LEVAQUIN levofloxacin Parenteral Products for Administration

LEVAQUIN Injection in Single-Use Vials

LEVAQUIN Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg of levofloxacin in Water for Injection. The 20 mL vials contain 25 mg of levofloxacin/mL. **THESE LEVAQUIN INJECTION SINGLE-USE VIALS MUST BE FURTHER DILUTED WITH AN APPROPRIATE SOLUTION PRIOR TO INTRAVENOUS ADMINISTRATION** (see **PHARMACEUTICAL INFORMATION:** *Compatible Intravenous Solutions*). The concentration of the resulting diluted solution should be 5 mg/mL prior to administration.

As with all parenteral products, the intravenous admixture should be inspected visually for clarity, discoloration, particulate matter, precipitate, and leakage, prior to administration, whenever solution and container permit. Units containing visible particles should be discarded.

Since no preservative or bacteriostatic agent is present in this product, aseptic techniques must be used in preparation of the final parenteral solution. **Since the vials are for single use only, any unused portion remaining in the vial should be discarded. When used for split dosing, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use** (see **PHARMACEUTICAL INFORMATION: Stability of LEVAQUIN Injection Following Dilution**).

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in single-use vials or infused simultaneously through the same intravenous line.** If the same intravenous

line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Prepare the desired dosage of levofloxacin according to the following chart:

Desired Dosage Strength	From Appropriate Vial, Withdraw Volume	Volume of Diluent	Infusion Time
250 mg	10 mL	40 mL	60 min
500 mg	20 mL	80 mL	60 min
750 mg	30 mL	120 mL	90 min

For example, to prepare a 500 mg dose using the 20 mL vial (25 mg/mL), withdraw 20 mL and dilute with a compatible intravenous solution to a total volume of 100 mL.

Compatible Intravenous Solutions

Any of the following intravenous solutions may be used to prepare a 5 mg/mL levofloxacin solution with the approximate pH values:

Intravenous Fluids	pH of LEVAQUIN Injection Solution
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte® 56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

LEVAQUIN Injection PREMIX in Single-Use Flexible Containers

LEVAQUIN Injection is also supplied in single-use flexible containers containing a premixed, ready-to-use levofloxacin solution in D_5W in the following formats:

- containers of 100 mL capacity containing 50 or 100 mL of PREMIXED solution
- containers of 150 mL capacity containing 150 mL of PREMIXED solution

NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY. Consequently, each 50 mL, 100 mL and 150 mL of PREMIXED solution contains the equivalent of 250 mg, 500 mg and 750 mg of levofloxacin (5 mg/mL), respectively in 5% Dextrose (D_5W).

This parenteral drug product should be inspected visually for clarity, discoloration, particulate matter, precipitate, and leakage prior to administration. Samples containing visible particles should be discarded.

Since the PREMIX flexible containers are for single use only, any unused portion should be discarded.

Since only limited data are available on the compatibility of levofloxacin intravenous injection with other intravenous substances, **additives or other medications should not be added to LEVAQUIN Injection in flexible containers or infused simultaneously through the same intravenous line.** If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN Injection with an infusion solution compatible with LEVAQUIN Injection and with any other drug(s) administered via this common line.

Instructions for the Use of LEVAQUIN Injection PREMIX in flexible containers

To open

1. Tear outer wrap at the notch and remove solution container.
2. Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.
3. Do not use if the solution is cloudy or a precipitate is present.
4. Use sterile equipment.
5. **WARNING: Do not use flexible containers in series connections.** Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration

1. Close flow control clamp of administration set.
2. Remove cover from port at bottom of container.
3. Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated.
   NOTE: See full directions on administration set carton.
4. Suspend container from hanger.
5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of LEVAQUIN Injection in PREMIX flexible containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

Stability of LEVAQUIN Injection Following Dilution

LEVAQUIN Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 24 hours when stored at or below 25°C, and for 72 hours when stored under refrigeration at 5°C in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass

bottles or plastic intravenous containers are stable for 6 months when stored at -20°C. **THAW FROZEN SOLUTIONS AT ROOM TEMPERATURE (25°C) OR IN A REFRIGERATOR (8°C). DO NOT FORCE THAW BY MICROWAVE IRRADIATION OR WATER BATH IMMERSION. DO NOT REFREEZE AFTER INITIAL THAWING.**

AVAILABILITY OF DOSAGE FORMS

Tablets

LEVAQUIN levofloxacin 250 mg Tablets are supplied as modified rectangular, film-coated, terra cotta pink tablets embossed “LEVAQUIN” on one side and “250" on the other.

LEVAQUIN levofloxacin 500 mg Tablets are supplied as modified rectangular, film-coated, peach tablets embossed “LEVAQUIN” on one side and “500" on the other.

LEVAQUIN levofloxacin 750 mg Tablets are supplied as modified rectangular, film-coated, white tablets embossed “LEVAQUIN” on one side and “750" on the other.

LEVAQUIN Tablets are packaged in bottles in the following configurations:

250 mg Tablets:

Bottles of 50 tablets

500 mg Tablets:

Bottles of 50 tablets

750 mg Tablets:

Bottles of 50 tablets

Single-Use Vials

LEVAQUIN levofloxacin for Injection is supplied in single-use vials. Each 20 mL vial contains a concentrated solution of 25 mg/mL with the equivalent of 500 mg of levofloxacin. **Single use vials require dilution prior to administration** (see **PHARMACEUTICAL INFORMATION: Preparation of LEVAQUIN levofloxacin Parenteral Products for Administration**).

Supplied in cartons of 1 vial

LEVAQUIN Injection PREMIX in Single-Use Flexible Containers

LEVAQUIN Injection is also supplied in single-use flexible containers containing a premixed, ready-to-use levofloxacin solution in D_5W in the following formats:

- containers of 100 mL capacity containing 50 or 100 mL of PREMIXED solution
- containers of 150 mL capacity containing 150 mL of PREMIXED solution

  Supplied in cases of 12 flexible containers

NO FURTHER DILUTION OF THESE PREPARATIONS IS NECESSARY. Consequently, each 50 mL, 100 mL and 150 mL of PREMIXED solution contains the equivalent of 250 mg, 500 mg and 750 mg of levofloxacin (5 mg/mL), respectively in 5% Dextrose (D_5W).

INFORMATION FOR THE PATIENT

LEVAQUIN* (levofloxacin) TABLETS

Before you start to take your medicine, please read this leaflet carefully, all the way through, as it contains important information.

Retain this leaflet for the duration of your treatment.

This leaflet does not list all the benefits and risks of LEVAQUIN tablets. The medicine described here can only be prescribed by a licensed healthcare professional.

If you have any questions about LEVAQUIN tablets, talk with your healthcare professional. Only your healthcare professional can determine if LEVAQUIN is right for you.

What is LEVAQUIN levofloxacin?

LEVAQUIN tablets are from a group of antibiotics known as quinolones. Quinolone antibiotics are used to treat lung, sinus, skin and urinary tract infections caused by certain germs called bacteria. LEVAQUIN tablets have been shown, in a large number of clinical trials, to be effective for the treatment of bacterial infections and can kill many of the types of bacteria that can infect the lungs, sinus, skin and urinary tract.

Sometimes, viruses rather than bacteria may infect the lungs and sinuses (for example, the common cold). LEVAQUIN tablets, like other antibiotics, does not kill viruses.

What ingredients are in LEVAQUIN tablets?

LEVAQUIN tablets contain the active (medicinal) ingredient levofloxacin and come in either 250 mg, 500 mg or 750 mg strengths. LEVAQUIN tablets are terra cotta pink for the 250 mg tablet, peach coloured for the 500 mg tablet, or white for the 750 mg tablet. All LEVAQUIN tablets also contain hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide and polysorbate 80. In addition, the 250 mg tablets also contain synthetic red iron oxide, and the 500 mg tablets also contain synthetic red and yellow iron oxides.

Who should not take LEVAQUIN tablets?

You should not take LEVAQUIN tablets if you have had an allergic reaction to any of the group of antibiotics known as quinolones. This includes antibiotics such as ofloxacin (FLOXIN*), ciprofloxacin (Cipro®), moxifloxacin hydrochloride (Avelox® Tablets), gatifloxacin (Tequin™ Tablets), alatrofloxacin mesylate (Trovan® I.V.), trovafloxacin mesylate (Trovan® Tablets), and norfloxacin (Noroxin®, Apo-Norflox®, Novo-Norfloxacin®, Riva-Norfloxacin®). If you have had any reaction to quinolones, you should discuss this with your doctor.

You should not take LEVAQUIN if you have had tendinitis or tendon rupture while taking quinolone antibiotics.

LEVAQUIN tablets are not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown. If you are pregnant, or planning to become pregnant while taking LEVAQUIN tablets, talk to your doctor before taking this medication.

LEVAQUIN tablets should not be used in children and adolescents below the age of 18 years.

What should you tell your doctor before taking LEVAQUIN tablets?

- You should tell your doctor if you have decreased kidney function.
- You should tell your doctor if you have epilepsy or have a history of seizures (convulsions).
- You should tell your doctor if you have had any problems with your heart rhythm, heart rate, or problems with low potassium.

How and when should I take LEVAQUIN tablets?

LEVAQUIN tablets should be taken once a day for 3, 5, 7, 10, or 14 days depending on your condition. Each tablet should be swallowed whole 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 that you are getting the full, sustained benefits from your medication so that your infection does not return, **you should complete the full course of medication**. Do not take more than the prescribed dose of LEVAQUIN tablets even if you missed a dose by mistake. You should not take a double dose.

Can I take LEVAQUIN tablets with other medicines?

Before taking your LEVAQUIN tablets, make sure you tell your doctor and pharmacist all the medications you are taking. Do not start a new medicine without first consulting a doctor or pharmacist.

It is important to let your doctor know all of the medicines you are using including some medications for arthritis (non-steroidal anti-inflammatory drugs), blood sugar medicines, drugs for any heart condition, and non-prescription drugs, because LEVAQUIN tablets may react with certain medications.

Taking warfarin (Coumadin®) and LEVAQUIN tablets together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your doctor.

Many antacids and multi-vitamins may interfere with the absorption of LEVAQUIN tablets and may prevent it from working properly. You should take LEVAQUIN tablets either two hours before or two hours after taking these products.

Some medicines such as erythromycin, clarithromycin, quinidine, procainamide, amiodarone, sotalol, cisapride, antipsychotics tricyclic antidepressants, and other medications may produce an effect on the electrocardiogram test. The risk of developing abnormal heartbeat may be increased when LEVAQUIN is taken with any of these medications. Do not take any of these medications with LEVAQUIN tablets unless your doctor tells you that it is alright.

What are the possible side effects of LEVAQUIN tablets?

LEVAQUIN tablets are generally well tolerated. The most common side effects caused by LEVAQUIN tablets, which are usually mild, include nausea, diarrhea, abdominal pain, dizziness, flatulence, rash and vaginitis in women. However, allergic reactions have been reported in patients receiving quinolones, including LEVAQUIN tablets, even after just one dose. If you develop hives, itching, skin rash, difficulty breathing or swallowing, swelling in the face, tongue or throat, or other symptoms of an allergic reaction, you should stop taking this medication and call your doctor.

LEVAQUIN may be associated with dizziness. You should know how you react to this drug before you operate an automobile, or machinery, or performing other activities requiring mental alertness or co-ordination.

Ruptures of shoulder, hand, or Achilles tendons have been reported in patients receiving quinolones, including LEVAQUIN tablets. If you develop pain, swelling, or rupture of a tendon you should stop taking LEVAQUIN tablets and contact your doctor.

Convulsions have been reported in patients receiving quinolone antibiotics including LEVAQUIN tablets.

Quinolones, including LEVAQUIN tablets, 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.

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. LEVAQUIN tablets have been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking LEVAQUIN tablets.

If you have diabetes and you develop a hypoglycemic reaction while taking LEVAQUIN tablets, you should stop taking LEVAQUIN tablets and call your doctor.

Some quinolones have been associated with lengthening of the heart beat on an electrocardiogram test, and with abnormal heart rhythm. Very rare cases of abnormal heart beat have been reported in patients while on LEVAQUIN, but these reports generally involved patients who had conditions that predisposed them to abnormal heart beat, or who have been taking other medicines that increase the risk of developing abnormal heart beat. If you develop heart palpitations (fast beating) or have fainting spells, you should stop taking LEVAQUIN tablets and call your doctor.

Eye abnormalities and abnormal vision have been reported in patients being treated with quinolones. The relationship of the drugs to these events has not been established.

These are not all the side effects that have been reported with LEVAQUIN. 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 doctor.

How to store LEVAQUIN Tablets

Store at room temperature (15°– 30°C) in well-closed containers.
Keep out of reach of the children.
Do not use after the expiry date. Generally, all expired medications should be returned to your pharmacist.

Other information

Remember to consult your doctor if you feel that LEVAQUIN is not helping you get better, or if you feel worse.

If you have taken too much LEVAQUIN (more than prescribed by your doctor), contact your doctor, nearest Emergency Department, or Poison Control Centre.

This information does not take place of discussion with your doctor or healthcare professional about your medical condition or your treatment.

MICROBIOLOGY

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antibacterial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other quinolone antibacterials involves inhibition of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV, enzymes required for DNA replication, transcription, repair, and recombination. In this regard, the L-isomer produces more hydrogen bonds and therefore, more stable complexes with DNA gyrase than does the D-isomer. Microbiologically, this translates into a 25- to 40-fold greater antibacterial activity for the L-isomer, levofloxacin, over the D-isomer. Quinolones rapidly and specifically inhibit bacterial DNA synthesis.

Levofloxacin has in vitro activity against a broad spectrum of gram-positive and gram-negative aerobic and anaerobic bacteria. Levofloxacin is often bactericidal at concentrations equal to or greater than the Minimum Inhibitory Concentrations (MIC). The in vitro activity of levofloxacin against clinical isolates is summarized in the following table.

In Vitro Activity of Levofloxacin Against Clinical Isolates

Organism	(# of isolates)	MIC (µg/mL)		
		50%	90%	Range
Acinetobacter baumannii	(57)	0.120	16.000	0.060- >16.000
Acinetobacter calcoaceticus	(48)	0.250	0.250	0.030- 64.000
Chlamydia pneumoniae	(10)	0.250	0.250	0.125- 0.500
Citrobacter diversus	(20)	0.030	0.030	0.015- 0.060
Citrobacter freundii	(50)	0.060	1.000	0.015- 8.000
Enterobacter spp.	(200)	0.060	0.500	≤0.008- >16.000
Enterobacter aerogenes	(44)	0.250	0.500	0.060- 2.000
Enterobacter agglomerans	(13)	0.250	0.250	0.060- 0.500
Enterobacter cloacae	(97)	0.250	0.500	0.025- 16.000
Enterococcus spp.	(162)	1.000	>16.000	0.500- >16.000
Enterococcus (Streptococcus) faecalis	(122)	1.000	16.000	0.250- 64.000
Escherichia coli	(817)	0.030	0.060	≤0.008- >16.000
Haemophilus influenzae	(94)	0.015	0.015	≤0.008- 0.030
Haemophilus parainfluenzae	(127)	0.250	0.250	0.015- 1.000
Haemophilus parahemolyticus	(12)	0.250	0.250	0.008- 0.250
Klebsiella spp.	(345)	0.060	1.000	0.015- 16.000
Klebsiella oxytoca	(43)	0.250	0.250	0.030- 2.000
Klebsiella pneumoniae	(225)	0.250	0.500	0.060- 18.000
Legionella pneumophila	(10)		0.030	0.0079- 0.030
Moraxella (Branhamella) catarrhalis	(110)	0.250	0.250	0.0150- 1.000
Morganella morganii	(43)	0.060	1.000	0.0150- >16.000
Mycoplasma pneumoniae	(60)	0.250	0.500	0.250- 0.500
Neisseria gonorrhoeae	(47)	≤0.008	0.016	≤0.008- 0.060
Neisseria meningitidis	(13)	0.250	0.250	0.250- 0.500
Proteus and Providencia spp.	(36)	0.060	1.000	0.015- >16.000
Proteus mirabilis	(123)	0.060	0.120	0.015- 4.000
Proteus vulgaris	(14)	0.250	0.250	0.250- 0.500
*Pseudomonas aeruginosa**	(378)	1.000	8.000	0.030- >16.000
Pseudomonas maltophilia	(17)	0.500	2.000	0.250- 4.000
Salmonella spp.	(10)	0.060	0.060	0.060- 0.250

Organism	(# of isolates)	MIC (µg/mL)		
		50%	90%	Range
Serratia spp.	(65)	0.120	0.500	0.030- >16.000
Serratia marcescens	(42)	0.250	1.000	0.125- 4.000
Staphylococcus aureus	(565)	0.250	0.500	0.125- 32.000
Staphylococcus aureus, methicillin-resistant (MRSA)**	(25)	0.250	0.500	0.120- 1.000
Staphylococcus aureus, methicillin-susceptible (MSSA)	(25)	0.250	0.500	0.120- 0.500
Staphylococcus aureus, oxacillin-resistant	(62)	8.000	>16.000	0.120- >16.000
Staphylococcus aureus, oxacillin-susceptible	(367)	0.120	0.500	0.030- 16.000
Staphylococcus epidermidis	(47)	0.250	8.000	0.250- 32.000
Staphylococcus epidermidis, methicillin-resistant (MRSE)	(14)	0.250	0.250	0.120- 0.500
Staphylococcus epidermidis, methicillin-susceptible (MSSE)	(12)	0.250	1.000	0.250- 1.000
Staphylococcus saprophyticus	(16)	0.500	1.000	0.250- 2.000
Stenotrophomonas maltophilia	(43)	2.000	16.000	0.250- 16.000
Streptococcus (Viridans group)	(8)	0.750	1.000	0.250- 1.000
Streptococcus (Group C)	(28)	0.500	1.000	0.250- 2.000
Streptococcus (Group G)	(34)	0.500	1.000	0.250- 2.000
Streptococcus agalactiae	(96)	1.000	2.000	0.500- 2.000
Streptococcus milleri	(35)	0.500	1.000	0.250- 4.000
Streptococcus pneumoniae	(99)	1.000	1.000	0.500- 2.000
Streptococcus pneumoniae, penicillin-susceptible (MIC≤0.06µg/mL)‡	(2699)	0.500	1.000	≤0.004- >8.000
Streptococcus pneumoniae, penicillin-resistant (MIC≥2.0µg/mL)‡	(538)	0.500	1.000	≤0.004- 2.000
Streptococcus pneumoniae, clarithromycin-susceptible (MIC≤0.25µg/mL)‡	(502)	0.500	1.000	0.250- >16.000
Streptococcus pneumoniae, clarithromycin-resistant (MIC≥1.0µg/mL)‡	(136)	1.000	2.000	0.12- 16.000
Streptococcus pneumoniae, erythromycin-resistant (MIC≥1.0µg/mL)‡	(27)	1.000	1.000	0.500- 16.000
Streptococcus pyogenes	(87)	0.500	1.000	0.250- 2.000
Streptococcus sanguis	(19)	1.000	2.000	0.250- 2.000

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

** Data obtained for isolates from Complicated Skin and Skin Structure clinical studies, and literature, indicate the MIC value has increased for MRSA (see INDICATIONS AND CLINICAL USE for approved organisms).

‡Based on NCCLS classification

Levofloxacin is not active against *Treponema pallidum* (see **WARNINGS: Sexually Transmitted Diseases**).

Resistance

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 other fluoroquinolones, some organisms resistant to other quinolones, including ofloxacin, may be susceptible to levofloxacin.

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution Techniques

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on a dilution method*[1] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorgansims other than *Haemophilus influenzae, Haemophilus parainfluenzae,* and *Streptococcus pneumoniae:*

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae:*[a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium*[1].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus pneumoniae*:[b]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b] These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25 - 2
Escherichia coli	ATCC 25922	0.008 - 0.06
Escherichia coli	ATCC 35218	0.015 - 0.06
Pseudomonas aeruginosa	ATCC 27853	0.5 - 4
Staphylococcus aureus	ATCC 29213	0.06 - 0.5
Haemophilus influenzae	ATCC 49247[c]	0.008 - 0.03
Streptococcus pneumoniae	ATCC 49619[d]	0.5 - 2

[c] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)*[1].

[d] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

Diffusion Techniques

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure*[2] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 µg levofloxacin to test the susceptibility of microorganisms to levofloxacin. Reports from the laboratory, providing results of the standard single-disk susceptibility test with a 5 µg levofloxacin disk, should be interpreted according to the following criteria:

For aerobic microorganisms other than *Haemophilus influenzae, Haemophilus parainfluenzae*, *Streptococcus pneumoniae* and *Neisseria gonorrhoeae:*

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:[e]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium* (HTM) [2].

The current absence of data on resistant strains precludes defining any categories other than "Susceptible". Strains yielding zone diameter results suggestive of a "Nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus pneumoniae:*[f]

Zone diameter (mm)	Interpretation
≥17	Susceptible (S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus pneumoniae* apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5 µg levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29 - 37
Pseudomonas aeruginosa	ATCC 27853	19 - 26
Staphylococcus aureus	ATCC 25923	25 - 30
Haemophilus influenzae	ATCC 49247[g]	32 - 40
Streptococcus pneumoniae	ATCC 49619[h]	20 - 25

[g] This quality control range is applicable to only *H. influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM)*[2].

[h] This quality control range is applicable to only *S. pneumoniae* ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

* REFERENCES

1. National Committee for Clinical Laboratory Standards: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, Fourth Edition, 1997.
2. National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Tests, Sixth Edition, 1997.

PHARMACOLOGY

Animal Pharmacology

A summary of the major findings obtained from animal pharmacology studies with levofloxacin is presented below:

Summary of Major Nonclinical Pharmacological Effects of Levofloxacin

System	Species	Major Findings
Central Nervous System	mouse	≥600 mg/kg, p.o., decreased spontaneous locomotor activity, CNS depression, decreased pinna reflex, decrease writhing response to acetic acid; increased incidences of strychnine-, pentylenetetrazol- and caffeine-induced convulsions; ≥200 mg/kg, i.v., convulsions after rapid injection, decreased spontaneous motor activity, muscle tone, posture, body temperature; increased respiratory rate; prolonged hexobarbital sleep time
	rat	At 200 mg/kg, i.v., inhibition of conditioned-avoidance response; At 200 mg/kg, i.p., increased spontaneous motor activity, lowered body posture, increased restlessness
	rabbit	At 200 mg/kg, p.o., decrease in body temperature
	cat	≥6 mg/kg, i.v., decreased spinal reflex; ≥30 mg/kg, i.v., increased EEG awake stage, seizure discharges
Autonomic Nervous System	cat	At 20 mg/kg, i.v., reduced contractile response of nictitating membrane to pre- and postganglionic stimulation; suppression of acetylcholine depressor response
Cardiopulmonary System	dog	≥6 mg/kg, i.v. bolus, decreases in blood pressure, left ventricular pressure, respiration depth; ≤10 mg/kg, i.v. infusion, no effect on blood pressure; ≥20 mg/kg, i.v. infusion, decrease in blood pressure, decrease in cardiac output and stroke volume; increase in serum histamine concentrations
Gastrointestinal System	mouse	At 200 mg/kg, i.v., inhibition of gastric propulsion
	rat	≥200 mg/kg, p.o., decrease in gastric fluid volume, total acidity, pepsin output; increase in gastric fluid pH; at 600 mg/kg, decrease in gastric emptying; at 200 mg/kg, i.v., decrease in gastric fluid volume, acid and pepsin output and gastric emptying; increase in gastric pH
Urinary Tract	rat	≥200 mg/kg, p.o., decrease in urinary volume and electrolyte excretion; at 200 mg/kg, i.v., decrease in urinary volume
Inflammation	rat	At 600 mg/kg, p.o., inhibition of carrageenan-induced foot edema
Isolated Smooth Muscles		On dog mesenteric, renal, femoral, and basilar arteries, inhibition of norepinephrine-induced contractions ≥10×10^{-6} M; competitive inhibition of phenylephrine-induced contractions of rabbit thoracic artery

In mice, the CNS stimulatory effect of quinolones is enhanced by concomitant administration of non-steroidal anti-inflammatory drugs.

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

Human Pharmacology

Pharmacokinetics

Absorption

Oral

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 a 500 mg tablet and a 750 mg tablet of levofloxacin is approximately 99% in both cases, demonstrating complete oral absorption of levofloxacin. Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral dosing regimens. After single oral doses of 250 to 1000 mg of levofloxacin to healthy subjects, plasma concentrations increase proportionally with the dose as shown (mean ± SD):

Oral Dose		Peak Plasma Concentration	Area Under the Curve
(mg)	n	(µg/mL)	($AUC_{0-\infty}$, µg.h/mL)
250	15	2.8 ± 0.4	27.2 ± 3.9
500	23	5.1 ± 0.8	47.9 ± 6.8
750	10	7.1 ± 1.4	82.2 ± 14.3
1000	10	8.9 ± 1.9	111.0 ± 20.8

Steady-state conditions are reached within 48 hours following 500 mg or 750 mg once-daily dosage regimens. The peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 and 0.5 µg/mL after the 500 mg doses, and 8.6 and 1.1 µg/mL after the 750 mg doses, respectively.

Oral administration with food slightly prolongs the time to peak concentration by approximately 1 hour and slightly decreases the peak concentration by approximately 14%.

Intravenous

Levofloxacin pharmacokinetics are linear and predictable after single and multiple i.v. dosing regimens. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean peak plasma concentration attained was 6.2 µg/mL after a 500 mg dose infused over 60 minutes and 7.99 µg/mL after

a 750 mg dose infused over 90 minutes. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosing regimen. The peak and trough plasma concentrations attained following multiple once-daily i.v. regimens were approximately 6.4 µg/mL and 0.6 µg/mL after the 500 mg doses, and 7.92 µg/mL and 0.85 µg/mL after the 750 mg doses, respectively.

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 (11.7 µg/g for a 750 mg dose) and in blister fluid (4.33 µg/g for a 500 mg dose) at approximately 3-4 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2. The blister fluid to plasma AUC ratio is approximately 1, following multiple once-daily oral administration of 750 mg and 500 mg levofloxacin to healthy subjects, respectively. Levofloxacin also penetrates into lung tissues. Lung tissue concentrations were generally 2- to 5-fold higher than plasma concentrations and range from approximately 2.4 to 11.3 µg/g over a 24-hour period after a single 500 mg dose. Levofloxacin also penetrates into cortical and spongiosa bone tissues in both the femoral head and distal femur. Peak levofloxacin concentrations in these tissues ranging from 2.4 to 15 µg/g were generally attained by 2 to 3 hours after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 µg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound (approximately 21 to 30 %) to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine, and does not invert metabolically to its enantiomer, D-ofloxacin. 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 urine within 48 hours, whereas less than 4% of the dose was recovered in 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

The major route of elimination of levofloxacin in humans is 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 or intravenously. 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, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Factors Influencing the Pharmacokinetics

Special Populations

Elderly

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 - 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary.

Pediatric

The pharmacokinetics of levofloxacin in pediatric patients have not been studied.

Gender

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when the differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects, and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race

The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 nonwhite. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Insufficiency

Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in patients with impaired renal function (creatinine clearance $\leq$ 80 mL/min). Dosage adjustment may be required in such patients to avoid levofloxacin accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating supplemental doses of levofloxacin are not required following hemodialysis or CAPD (see **ACTION AND CLINICAL PHARMACOLOGY: Pharmacokinetics**, **PRECAUTIONS: Renal,** and **DOSAGE AND ADMINISTRATION**).

Plasma Ratio

Comparison of the expected steady-state AUC values[a] in renally impaired patients relative to those in patients with normal renal function:

	Creatinine Clearance 50-80 mL/min receiving 500 mg q24h	Creatinine Clearance 20-49 mL/min receiving 250 mg q24h	Creatinine Clearance < 20 mL/min receiving 250 mg q48h
AUC value relative to patients with normal renal function receiving 500 mg q24h	172%	183%	139%
AUC value relative to patients with normal renal function receiving 500 mg q12h	89%	94%	71%

[a]Values were extrapolated from the mean levofloxacin plasma concentration-time data in subjects with normal renal function (n = 23) and subjects with impaired renal function (n = 3 for Cl_{Cr} 50 - 80 mL/min, n = 8 for Cl_{Cr} 20 - 49 mL/min, and n = 6 for Cl_{Cr} < 20 mL/min).

Urine Concentrations

The mean ± SD concentrations (µg/mL) of levofloxacin in the urine following a 500 mg p.o. dose of levofloxacin in subjects with impaired renal function are summarized as follows[a]:

Collection Interval	Cl_{Cr} 50-80 mL/min	Cl_{Cr} 20-49 mL/min	Cl_{Cr} < 20 mL/min
	n[b]=3	n=8	n=6
0 ___ 6 h	185 ± 61.7	98.1 ± 48.1	66.5 ± 27.3
6 ___ 12 h	91.6 ± 24.4	75.2 ± 22.1	39.0 ± 23.1
12 ___ 24 h	156 ± 183	58.6 ± 31.1	29.5 ± 20.7
24 ___ 36 h	49.7 ± 16.2	44.1 ± 10.6	< 25
36 ___ 48 h	< 25	< 25	< 25

[a]Limit of quantitation = 25 µg/mL
[b] n = number of subjects

Expected steady-state urinary concentrations (µg/mL) of levofloxacin in renally impaired patients with the recommended adjusted dose regimen in the treatment of complicated UTI and acute pyelonephritis[a]:

Collection Interval	Cl_{Cr} 50-80 mL/min receiving 250 mg q24h	Cl_{Cr} 20-49 mL/min receiving 250 mg q24h	Cl_{Cr} < 20 mL/min receiving 250 mg q48h
0 ___ 6 h	161	103	54
6 ___ 12 h	61	76	29
12 ___ 24 h	40	58	24
24 ___ 36 h	--	--	23
36 ___ 48 h	--	--	16

[a] Values were extrapolated from the mean pharmacokinetic profiles in subjects with impaired renal function (n= 12 for Cl_{Cr} 50 - 80 mL/min, n = 8 for Cl_{Cr} 20 - 49 mL/min, and n = 6 for Cl_{Cr} < 20 mL/min).

Hepatic Insufficiency

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Bacterial Infection

The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

HIV Infection

The pharmacokinetics of levofloxacin in HIV seropositive subjects (with CD4 cell counts ranging from 17 to 772) are comparable to those observed in healthy subjects.

Drug-Drug Interactions

The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, zidovudine and antacids has been evaluated (see **PRECAUTIONS: Drug Interactions**).

Studies Measuring the Effects on QT and Corrected QT (QTc) Intervals

Two double-blind, placebo-controlled studies assessing the effect of levofloxacin on QTc intervals in healthy male and female volunteers 18-84 years of age were conducted. Each had a four-treatment crossover, single-dose study design. One study evaluated dose-response. The other was a comparative study that involved measuring the effects of doses of levofloxacin and two other fluoroquinolones. In this comparative study, subjects were given twice the doses of these antibiotics that are recommended for the treatment of otherwise healthy subjects with community-acquired pneumonia. In both trials, no effect on QT intervals compared to placebo was evident at any of the doses of levofloxacin studied (top panels of figure A and figure B).

Dose escalation study (Figure A): In this trial, the mean change in the average QTc interval (calculated from measurements taken every half hour for two hours and at 4, 8, 12 and 24 hours after treatment) from the baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) was a decrease of 1.84 msec after treatment with 500 mg, an increase of 1.55 msec after treatment with 1000 mg of levofloxacin and an increase of 6.40 msec after treatment with 1500 mg. The change in QTc interval at Cmax (calculated using the Bazett formula) after treatment with 500 mg of levofloxacin was not significantly different from that measured after treatment with placebo. In this trial, the mean change in the QTc (Bazett) at Cmax from baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) was –3.20 msec after treatment with 500 mg of levofloxacin, 7.82 msec after treatment with 1000 mg of levofloxacin and 10.58 msec after treatment with 1500 mg of levofloxacin.

Comparative, placebo-controlled study (Figure B; only levofloxacin and placebo data shown): In this study, the mean change in the average QTc interval (calculated from measurements taken every half hour for four hours and at 8, 12 and 24 hours after treatment) from the baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) was 3.58 msec after treatment with 1000 mg levofloxacin. In this study, the change in the QTc (Bazett) at Cmax from a baseline QTc (calculated as the average QTc measured 24, 20, 16 hours and immediately before treatment) was 5.32 msec after treatment with 1000 mg of levofloxacin.

FIGURE A
Mean QT and QTc Bazett versus Time after Dose of Placebo, 500 mg, 1000 mg or 1500 mg Levofloxacin (Dose Escalation Study n=48)

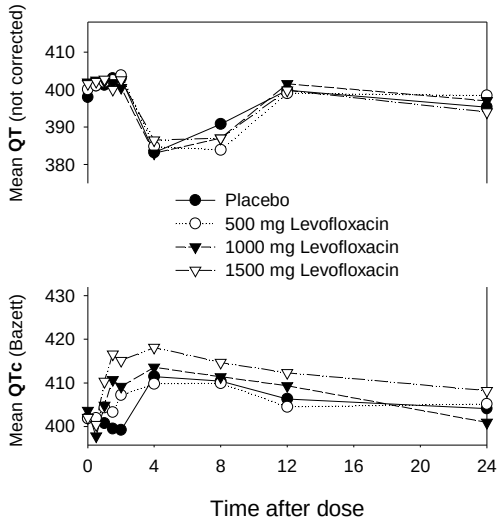
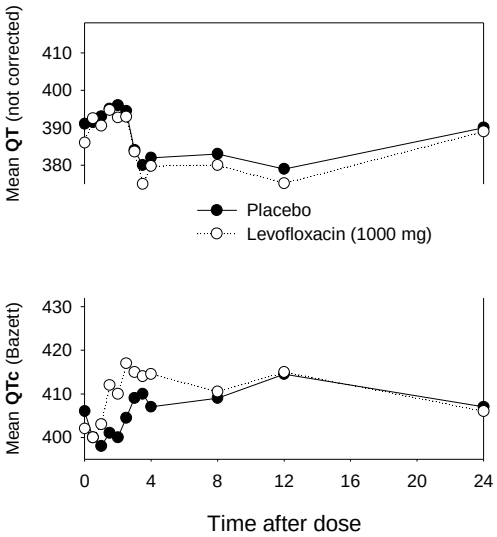


FIGURE B
Mean QT and QTc Bazett versus Time after Dose of Placebo or 1000 mg of Levofloxacin (Comparative Study n=48)



Clinical Studies

Community Acquired Pneumonia

7 to 14 Day Treatment Regimen

In three North American clinical studies, of 655 patients treated with levofloxacin for community-acquired pneumonia, 45 clinically and microbiologically evaluable patients were defined as severely ill by study criteria and met American Thoracic Society criteria for severe (American Thoracic Society, 1993). Clinical success (cure and improvement) was achieved in 98% of these 45 patients. Data on the treatment of patients with severe Legionella pneumonia is limited to one patient.

Data on the treatment of community-acquired pneumonia due to penicillin-resistant *S. pneumoniae* is limited to 12 evaluable patients from the combined clinical trials database. Of these, 4 were considered to have been severe. All 12 patients achieved clinical success (see **MICROBIOLOGY**).

5-Day Treatment Regimen

To evaluate the safety and efficacy of higher dose and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicentre study comparing levofloxacin 750 mg, i.v. or p.o., q.d. for five days or levofloxacin 500 mg i.v. or p.o., q.d. for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 92.4% (183/ 198) in the levofloxacin 750 mg group and 91.1% (175/192) in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-7.0, 4.4]. In the clinically evaluable population (31-38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin 750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in the table below:

	Eradication rate
Penicillin susceptible *S. pneumoniae*	19/22
Haemophilus influenzae	12/13
Haemophilus parainfluenzae	12/12
Mycoplasma pneumoniae	32/34
Chlamydia pneumoniae	20/22
Legionella pneumophila	12/12

Acute Bacterial Exacerbation of Chronic Bronchitis

5 Day Treatment Regimen

Study demographics and trial design

Summary of Patient Demographics for Clinical Trial in Acute Bacterial Exacerbation of Chronic Bronchitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects [a] (n=number)	Mean age (Range)	Gender male/female
CAPSS-197	randomized, blinded, non-inferiority study	**LFX**: oral levofloxacin 750 mg once daily for 5 days **AMX/CL**: oral amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days	**LFX**: n=187 **AMX/CL**: n=182	**LFX**: 58 (18-91) **AMX/CL**: 59 (20-85)	**LFX**: 93/94 **AMX/CL**: 88/94

[a] From ITT population. Study subjects were characterized by FEV_1<50% predicted, or FEV_1 between 50% and 65% predicted, with ≥4 exacerbations in the preceding 12 months and/or the presence of significant co-morbidity. About half (48.2%) of the subjects were current smokers, with a mean pack-year history of 42.4.

Study results

Results of Study CAPSS-197 in Acute Bacterial Exacerbation of Chronic Bronchitis

Primary Endpoints	levofloxacin 750 mg once daily for 5 days	amoxicillin 875 mg / clavulanate 125 mg twice daily for 10 days	difference [c]	95% Confidence Interval [d]
Clinical response [a]	Success [b]: 95/120 (79.2%); Non-Success: 25/120 (20.8%)	Success [b]: 103/126 (81.7%) Non-Success: 23/126 (18.3%)	2.6%	(-7.8, 12.9)

[a] 17 to 26 days after the first dose of study drug for clinical evaluable subjects
[b] success rates include the clinical response category of cured and improved
[c] difference in success rates
[d] two-sided 95% CIs (with continuity correction) around the difference (amoxicillin/clavulanate minus levofloxacin) in clinical success rates

Microbiologic Eradication Rates for Microbiologically Evaluable Population

Pathogen	Levofloxacin		Amoxicillin/clavulanate	
	n/N (%)		n/N (%)	
Staphylococcus aureus	4/5	(80.0)	3/5	(60.0)
Streptococcus pneumoniae	16/18	(88.9)	10/13	(76.9)
Haemophilus influenzae	25/30	(83.3)	20/20	(100.0)
Haemophilus parainfluenzae	18/20	(90.0)	15/18	(83.3)
Moraxella catarrhalis	10/12	(83.3)	16/19	(84.2)

TOXICOLOGY

The potential toxicity of levofloxacin has been evaluated in acute, sub-chronic, carcinogenicity, mutagenicity, reproduction and teratology, and special toxicity studies.

Acute Toxicity

Summary of the acute toxicity studies is presented in the following table.

STRAIN/ SPECIES	# ANIMAL/ GROUP	ROUTE	LD_{50} mg/kg	SUMMARY TOXIC SIGNS
Mouse	M-10 F-10	p.o.	1881 1803	↓ locomotor activity, ptosis, respiratory depression, tremor, convulsion
Mouse	M-10	p.o.	1943	↓ locomotor activity, ptosis, prostration, tremor, convulsion
Rat	M-10 F-10	p.o.	1478 1507	salivation, ptosis, ↓ locomotor activity, tremor, convulsion, respiratory depression
Rat	M-10	p.o.	1754	
Monkey	F-2	p.o.	>250	soft stool, transient ↓ platelet count and ↑ bw at 250 mg/kg, transient ↑ bilirubin, ↓ bw, and emesis at 500 mg/kg
Mouse	M-10 F-10	i.v.	268 323	↓ locomotor activity, ptosis, abnormal posture, tachypnea, convulsion, dyspnea
Mouse	M-5	i.v.	244	symptoms prior to death: tachypnea, collapse, dyspnea, convulsions, respiratory arrest. In survivors, ↓ locomotor activity and collapse
Rat	M-10 F-10	i.v.	423 395	↓ locomotor activity, prostration followed by respiratory depression, tachypnea, dyspnea, convulsion, tremor, salivation
Dog	F-2	i.v.	200	salivation, dyspnea, tonic and clonic convulsion, death from respiratory arrest at 200 mg/kg, lacrimation, vomiting, lethargy, and tremors. ↑ RBC, WBC, ALT and ALP, and ↓ P on Day 2. Values returned to normal by Day 8.
Monkey	F-2	i.v.	>200	at 200 mg/kg - ptosis, vomiting, ↓ locomotor activity, prostration and anorexia, ketone urine, proteinuria, ↓ glucose. Ptosis and emesis at 100 mg/kg

Signs of acute toxicity with metabolites (desmethyl and N-oxide) were similar to that of levofloxacin and were produced at doses significantly greater than would be encountered with therapeutic use.

Sub-Chronic Toxicity

Species, Age/Grp/No., Sex/Grp	Route, Dosage, Duration	Results
Rat 4-6 wk old 4 grp 10 ♀ & 10 ♂/ grp	p.o. 0, 50, 200, 800 4 weeks	**Lethality:** No treatment-related deaths. **Clin Obs:** Salivation, body staining, transient pallor and hypothermia at 800 mg/kg. Transient ↓ fc in treated ♂ and ↓ bw gain during week 1 in ♂ at 800 mg/kg. **Clin Path:** ↑ WBC due to ↑ in lymphocytes at 800 mg/kg. PMNs ↓ in treated ♀ and at 50 and 200 mg/kg in ♂. ↓ K^+, Cl^-, and urea and ↑ P and ALT (primarily at 800 mg/kg). Higher M:E ratio at 800 mg/kg. **Micro:** ↓ relative heart weights at 800 mg/kg and ↑ cecal weights at 200 and 800 mg/kg. Slight vacuolization and minimal hypertrophy of hepatocytes at 800 mg/kg and arthropathy (minor) at 800 mg/kg. NOAEL = 200 mg/kg/day. TI = 2.8
Rat 4-5 wk old 4 grp 20 ♀ & 20 ♂/ grp	p.o. 0, 20, 80, 320 26 wk	**Lethality:** No treatment-related deaths. **Clin Obs:** Salivation, ↑ large fecal pellets, and stained haircoat mainly at 320 mg/kg. ↑ fc at 80 and 320 mg/kg, ↑ food conversion ratios in ♀ at 320 mg/kg. **Clin Path:** ↓ PMNs in all treated rats, ↑ glucose (treated ♂), ↓ triglycerides (320 mg/kg ♀), ↓ ß-globulin (treated rats),↓ α-globulin (treated ♀), ↓ Cl^- (320 mg/kg rats and 80 mg/kg ♀),↓ total protein (80 and 320 mg/kg ♂), and ↑ urinary pH at 80 and 320 mg/kg. **Micro:** Dosage-related ↑ cecal weight, elongated and/or distended ceca and engorged goblet cells of the cecal mucosa. Changes in intestinal flora and lower nutrient absorption in the intestines probably responsible for most changes. No arthropathy. NOAEL = 20 mg/kg/day. TI = 2.8
Rat 6 wk old 5 grp 10 ♀ & 10 ♂/ grp	diet 0, 100, 200, 400, 800 13 wk	**Lethality:** No deaths. **Clin. Obs:**↓ bw at 400 and 800 mg/kg. **Clin Path:** ↓ total protein (≥200 mg/kg), globulin, and triglycerides (at 800 mg/kg ♂ only). ↑ ALP at 800 mg/kg (♀). **Micro:** ↓ absolute liver weight ≥400 (♂),↑ cecal weight and cecal distension (≥100). No arthropathy. NOAEL = 100 mg/kg/day. TI = 14
Rat 4 wk old 3 grp, 5 ♂/ grp	i.v. 0, 20, 100 10 days	NSF
Rat 4 wk old 4 grp, 4 ♂/ grp	i.v. 0, 10, 40, 160 2 wk	**Lethality:** No mortality. **Clin Obs:** NSF. **Clin Path and Micro:** Crystalluria,↑ cecal weight and ↓ (mild) AST and ALT at 160 mg/kg. No arthropathy. NOAEL = 40 mg/kg/day. TI = 5.6
Rat 5 wk old 4 grp 10 ♀ & 10 ♂/ grp	i.v. 0, 20, 60, 180 4 wk	**Lethality:** No mortality. **Clin Obs:** Transient ↓ spontaneous activity, blepharoptosis (♂), ↓ bw gain and fc, and swelling at the injection site at 180 mg/kg. **Clin Path:** ↓ total protein, albumin, A/G ratio, cholinesterase activity, urinary protein, and RBC.↑ WBC, retic, and fibrinogen at 180 mg/kg. Crystalluria. **Micro:** ↓ weights of thymus, liver, heart, ovaries, and brain due to↓ bw gain. ↑ cecal weight at 60 and 180 mg/kg. Arthropathy at 60 and 180 mg/kg. NOAEL = 20 mg/kg/day, TI = 2.8.
Rat 6 wk old 4 grp 10 ♀ & 10 ♂/ grp	i.v. 0, 10, 30, 90 13 wk	**Lethality:** None. **Clin Obs:** Slight ↓ fc at 30 and 90 mg/kg (♂). **Clin Path:** Mild↓ total protein, phospholipids, and cholesterol at 90 mg/kg (♂) due to ↓ fc. Mild ↑ A/G and albumin at 30 and 90 mg/kg (♂). Crystalluria at 30 and 90 (♂) and 90 mg/kg (♀). **Micro:** ↑ cecal weight, arthropathy (mild) at 90 mg/kg. NOAEL = 30 mg/kg/day. TI = 4.2
Dog 4-5 mo old 5 grp 3 ♂/ grp	i.v. 0, 2, 4, 15, 60 2 wk	**Lethality:** None. **Clin Obs:** Histamine-like effects at 15 and 60 mg/kg,↓ bw gain and fc at 60 mg/kg. **Clin Path:** ↑ plasma fibrinogen and urine specific gravity; ↓ serum Fe. **Micro:** ↓ absolute liver weight at 60 mg/kg and ↓ absolute and relative testes weight at 4, 15, and 60 mg/kg; and thrombus formation in injected vessels at 60 mg/kg, arthropathy and delayed testicular maturation at ≥ 4 mg/kg. NOAEL = 2 mg/kg/day. TI = 0.28
Dog 18 mo old 3 grp 3 ♂/ grp	i.v. 0, 10, 30 2 wk	**Lethality:** None. **Clin Obs:** Histamine-like effects and ↓ activity at 10 and 30 mg/kg. Signs subsided by 30 min post-administration except ↓ activity. **Clin Path:** NSF. **Micro:** NSF. NOAEL for arthropathy = 30 mg/kg/day. TI = 4.2
Dog 7-8 mo old 4 grp 3 ♀ & 3 ♂/ grp	infusion 0, 3, 10, 30 4 wk	**Lethality:** None. **Clin Obs:** Histamine-like effects in a dosage-related manner. **Clin Path:** NSF. **Micro:** Arthropathy at ≥10 mg/kg/day. NOAEL = 3 mg/kg/day. TI = 0.42

Species, Age/Grp/No., Sex/Grp	Route, Dosage, Duration	Results
Monkey 2-4 yr old 4 grp 3 ♀ & 3 ♂/ grp	p.o. 0, 10, 30, 100 4 wk	**Lethality:** None. **Clin Obs and Clin Path:** Salivation and diarrhea at 100 mg/kg. Some animals occasionally had what appeared to be blood in the urine. Slight bw losses, unusually large adrenal glands in one monkey and low urinary pH in two monkeys at 100 mg/kg/day. **Micro:** NSF. NOAEL = 30 mg/kg/day. TI = 4.2
Monkey 2-4 yr old 4 grp 4 ♀ & 4 ♂/ grp	p.o. 0, 10, 25, 62.5 26 wk	**Lethality:** None. **Clin Obs:** ↓ fc in one high-dosage male during the first half of the study. **Clin Path and Micro:** NSF. NOAEL = 62.5 mg/kg/day. TI = 8.75
Monkey 2-4 yr old 4 grp 3 ♀ & 3 ♂/ grp	i.v. 0, 10, 25, 63 4 wk	**Lethality:** None. **Clin Obs:** Loose stools and slightly↓ wc at 25 and 63 mg/kg and ptosis, occasional quietness, and↓ fc (♀) at 63 mg/kg. **Clin Path:** NSF. **Micro:** NSF. NOAEL = 10 mg/kg/day. TI = 1.4

Dosage = mg/kg/day; Clin Obs = clinical observations; Clin Path = clinical pathology; Micro = macroscopic and microscopic findings;
NOAEL = No Observable Adverse Effect Level; NSF = No Significant Findings; TI = Therapeutic Index - relationship of toxic dose to the projected human dose (calculation based on maximum daily dose of 500 mg and body weight of 70 kg);
ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; A/G = albumin/globulin;
fc = food consumption; wc = water consumption; bw = body weight;
RBC = red blood cells; WBC = white blood cells; retic = reticulocyte; PMN = neutrophil; M:E = myeloid:erythroid;
K^+ = potassium; Cl^- = chloride; P = phosphorus; Fe = iron.

Carcinogenicity

Levofloxacin exhibited no carcinogenic or tumorigenic potential after dietary administration of 10, 30 or 100 mg/kg/day for 2 years in a rat carcinogenicity study. The highest dose was 1.4 or 6.7 times the highest recommended human dose (750 mg) based on surface area or body weight, respectively. The mean levofloxacin plasma concentration in the 2-year rat bioassay (at 100 mg/kg/day) was 34% of the human steady-state concentration after 500 mg b.i.d. dosing. In a 2-stage multiple organ carcinogenesis model in rats, levofloxacin at a dosage level of approximately 668 mg/kg/day in diet for 16 weeks did not promote the development of preneoplastic or neoplastic lesions after pretreatment with a number of wide spectrum carcinogens.

Mutagenicity

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assays (*S. typhimurium* and *E. coli*), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis and the mouse sister chromatid exchange (SCE) assays. It was positive in the in vitro chromosomal aberration (CHL cell line) and SCE assays (CHL/IU cell line).

Reproduction and Teratology

Segment I: Fertility and Reproductive Performance Studies

Study[a]	Parental Toxicity	Embryo/Fetal Toxicity	Teratogenicity
Oral gavage, rat 0, 10, 60, 360 mg/kg/day 24/sex/group	salivation (at 60 mg/kg mostly ♂ and at 360 mg/kg ♀ & ♂) and soft stool at 360 mg/kg; ↑ wc at 360 mg/kg for ♂ and ≥60 mg/kg for ♀; ↓ in placental weights at 360 mg/kg. No effect on mating performance.	No effect on intrauterine survival or fetal development.	None
Intravenous, rat 0, 10, 30, 100 mg/kg/day 24/sex/group	swollen tail, soft feces, and urinary incontinence at 100 mg/kg in ♂ and ♀. In females, ↓ bw gain and fc (wk 1 only) at 100 mg/kg. In males, ↓ bw gain ≥30 and slight ↓ fc at all levels, enlarged cecum ≥30 mg/kg. No effect on reproductive performance. NOAEL = 10 mg/kg/day for ♂ rats, 30 mg/kg/day for ♀ rats.	No effect on intrauterine survival or development. Slight non-dose-related ↑ in resorptions. NOAEL = 100 mg/kg/day for in utero exposure for rat fetuses.	None

wc = water consumption; bw = body weight; fc = food consumption

[a] In both studies, males (8 weeks old) were administered levofloxacin daily for 9 weeks prior to mating, throughout the mating period, and until necropsy. The females (11-12 weeks old) were treated daily for 2 weeks prior to mating, throughout the mating period, and for 7 days after copulation.
NOAEL = No Observable Adverse Effect Level.

SEGMENT II - Teratogenicity

Study[a]	Maternal Toxicity	Embryo/Fetal Toxicity	Teratogenicity
Oral gavage, rat 0, 10, 90, 810 mg/kg/day 36♀/group	salivation, piloerection, alopecia, and poor hair coat, soft stool, hyperuresis and/or watery eyes at 90 mg/kg and 810 mg/kg. ↓ bw gain at 810 mg/kg, ↓ fc ≥90 mg/kg, ↑ wc at 810 mg/kg, enlarged cecum ≥ 90 mg/kg. NOAEL = 10 mg/kg.	No effect on survival and weaning rate, sexual maturation, development or reproductive performance of F_1 generation. ↓ mean bw for pups at birth (♂ and ♀) on Days 63-77 postpartum (♀) at 810 mg/kg. ↑ fetal mortality, and ↓ fetal weight at 810 mg/kg. Maternal toxicity at 810 mg/kg led to delayed ossification of sternum, metatarsal, proximal phalange, and caudal vertebrae.	None
Intravenous, rat 0, 10, 40, 160 mg/kg/day 36♀/group	↓ fc at 40 mg/kg (Days 7-12 only) and at 160 mg/kg. Swollen tails (inj. site) and ↑ wc at 160 mg/kg. NOAEL = 10 mg/kg for dams.	Maternal toxicity led to delayed ossification of sternum and caudal vertebrae. No effect other than delayed ossification was observed. NOAEL = 40 mg/kg for fetuses, ≥160 mg/kg for pups.	None
Oral gavage, rabbit 0, 5, 16, 50 mg/kg/day 16♀/group	↓ fc and bw gain at 50 mg/kg, transient ↓ fc at 16 mg/kg, ↑ number placental remnants at 50 mg/kg, 4 dams aborted. NOAEL = 5 mg/kg/day for dams.	No adverse effects. NOAEL = 50 mg/kg/day for fetuses.	None
Intravenous, rabbit 0, 6.25, 12.5, 25 mg/kg/day 20♀/group	transient ↓ bw and fc at 25 mg/kg early in gestation (Days 6-9). NOAEL = 12.5 mg/kg/day for maternal toxicity.	No adverse effects. NOAEL = 25 mg/kg/day for developmental toxicity.	None

bw = body weight; wc = water consumption; fc = food consumption; inj. = injection

[a] In both rat studies, the rats were dosed from Day 7 to Day 17 of gestation.

NOAEL = No Observable Adverse Effect Level

Segment III: Perinatal and Postnatal

Study	Maternal Toxicity	Embryo/Fetal Toxicity	Parturition/Neonatal Growth and Survival
Oral gavage, rat 0, 10, 60, 360 mg/kg/day 24♀/group Dosed daily from Day 17 of gestation to Day 21 of lactation	salivation, diarrhea and soft feces at 360 mg/kg, salivation in some at 60 mg/kg, ↓ fc at 60 mg/kg during gestation and lactation (Days 14-18), ↓ fc during gestation and ↑ fc during lactation at 360 mg/kg, ↓ wc on 2 days during gestation and ↑ wc during lactation at 360 mg/kg. NOAEL = 10 mg/kg for dams.	No effects on either F_1 or F_2 generation. NOAEL = 360 mg/kg for pups.	No effects

NOAEL = No Observable Adverse Effect Level

Special Studies

Arthropathic Potential

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested (see **WARNINGS**). In juvenile rats, 7 days of oral administration of 300 mg/kg/day levofloxacin results in blister and cavity formation in articular cartilage. In juvenile dogs (4 months old), 7 days of oral administration of 10 mg/kg/day levofloxacin produces blister formation, cavitation, and increased synovial fluid of diarthroidal joints. In young immature dogs (13 months old), blister formation and cavitation of the arthritic joint were observed in 1/3 dogs following oral administration of 40 mg/kg/day levofloxacin for 7 days.

In long-term multidose studies, arthropathy in rats was observed after oral administration of 800 mg/kg/day for 4 weeks, after intravenous administration at 60 mg/kg/day for 4 weeks and 90 mg/kg/day for 13 weeks. Arthropathic lesions were observed in 4-month-old dogs following 4 mg/kg/day intravenous administration for 2 weeks and in 7-8 month-old dogs following 10 mg/kg/day intravenous administration for 4 weeks. No arthropathy was observed following 2-week intravenous dosing at dosages up to 30 mg/kg/day in young adult dogs (18 months old).

Phototoxicity

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin but less phototoxicity than some of the other quinolones tested. A single oral administration of 800 mg/kg levofloxacin followed by UVA exposure has been shown to result in ear erythema and swelling.

Crystalluria

When tested in rats with 20, 60, 120 or 180 mg/kg of levofloxacin, crystalluria has been observed in some intravenous rat studies; urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

Cardiac Effects

Levofloxacin exhibits a weak interaction with the human HERG channel. The IC_{50} for levofloxacin in inhibiting human HERG K^+ channel is 915 µM. At therapeutic doses of 250, 500, and 750 mg levofloxacin, the peak unbound plasma concentrations ranged from 6 µM for a single oral levofloxacin dose of 250 mg to 12 µM and 15 µM for 500 and 750 mg levofloxacin doses, respectively.

Studies in rabbit Purkinje fibers and studies in guinea pig right ventricular myocardium revealed no detectable effect on action potential duration with levofloxacin at concentrations up to100 µM.

The potential for levofloxacin to induce torsades de pointes was examined in a canine model of chronic high-degree atrioventricular block. Oral administration of levofloxacin at 6 and 60 mg/kg induced no ventricular arrhythmias. Monophasic action potential duration (MAP_{90}) was not significantly affected by levofloxacin 0.3 and 3.0 mg/kg IV.

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