PRODUCT MONOGRAPH

[Pr] phl-LEVOFLOXACIN

Levofloxacin

Tablets 250 mg, 500 mg and 750 mg
(as Levofloxacin hemihydrate)

Antibacterial Agent

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Date of Revision:
February 20, 2013

Submission Control No: 162069

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[Pr] phl-LEVOFLOXACIN
Levofloxacin Tablets
(as Levofloxacin Hemihydate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 250 mg, 500 mg, 750 mg	*For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

phl-LEVOFLOXACIN Tablets are indicated for the treatment of adults with bacterial infections caused by susceptible strains of the designated microorganisms in the infections listed below.

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 ***Product Monograph Part II*: CLINICAL TRIALS**).

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* (see **DOSAGE AND ADMINISTRATION** and ***Product Monograph Part II:*** **CLINICAL TRIALS**).

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* (see **DOSAGE AND ADMINISTRATION** and ***Product Monograph Part II:*** **CLINICAL TRIALS**).

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.

Geriatrics (≥ 65 years of age):
Drug absorption appears to be unaffected by age. Dose adjustment based on age alone is not necessary (see **WARNINGS AND PRECAUTIONS, Special Populations** and **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics (< 18 years of age):
Safety and effectiveness in children under 18 years of age have not been established (see **WARNINGS AND PRECAUTIONS, Special Populations, Special Populations and Conditions**).

CONTRAINDICATIONS

phl-LEVOFLOXACIN (levofloxacin) tablets are contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.

Levofloxacin is also contraindicated in persons with a history of tendinitis or tendon rupture associated with the use of any member of the quinolone group of antimicrobial agents.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Levofloxacin has been shown to prolong the QT interval of the electrocardiogram in some patients (see **WARNINGS AND PRECAUTIONS, Cardiovascular**).
- Serious hypersensitivity and/or anaphylactic reactions have been reported in patients receiving quinolone therapy, including levofloxacin (see **WARNINGS AND PRECAUTIONS, Immune**).
- Seizures may occur with quinolone therapy. phl-LEVOFLOXACIN should be used with caution in patients with known or suspected CNS disorders which may predispose to seizures or lower the seizure threshold (see **WARNINGS AND PRECAUTIONS, Neurologic**).
- Fluoroquinolones, including levofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid phl-LEVOFLOXACIN in patients with a known history of myasthenia gravis (see **WARNINGS AND PRECAUTIONS**, **Musculoskeletal**).
- Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see **WARNINGS AND PRECAUTIONS**, **Musculoskeletal**).

General

The oral 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 ***Product Monograph Part II*: TOXICOLOGY**).

Although levofloxacin is soluble, adequate hydration of patients receiving 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 **ADVERSE REACTIONS**).

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.

Cardiovascular
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 ***Product Monograph Part II*: DETAILED PHARMACOLOGY, Human Pharmacology, Studies Measuring Effects on QT and Corrected QT (QTc) Intervals**).

Endocrine and Metabolism
Disturbances of Blood Glucose
Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with the use of quinolones, including levofloxacin. In patients treated with levofloxacin, some of these cases were serious. Blood glucose disturbances were 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**). Serious hypoglycaemia and hyperglycemia have also occurred in patients without a history of diabetes.

Gastrointestinal
***Clostridium difficile*-associated disease**
Clostridium difficile-associated disease (CDAD) has been reported with use of many antibacterial agents, including levofloxacin. CDAD may range in severity from mild diarrhea to fatal colitis. It is important to consider this diagnosis in patients who present with diarrhea or symptoms of colitis, pseudomembranous colitis, toxic megacolon, or perforation of the colon subsequent to the administration of any antibacterial agent. CDAD has been reported to occur over 2 months after the administration of antibacterial agents.

Treatment with antibacterial agents may alter the normal flora of the colon and may permit overgrowth of *Clostridium difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. CDAD may cause significant morbidity and mortality. CDAD can be refractory to antimicrobial therapy.

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

Hepatic

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

Immune

Hypersensitivity

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, including acute 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**).

Musculoskeletal

Tendinitis

Rupture of the shoulder, hand and Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including Levofloxacin. phl-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 tendinitis or tendon rupture has been confidently excluded. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. phl-LEVOFLOXACIN should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug (see **ADVERSE REACTIONS)**.

Levofloxacin should not be used in patients with a history of tendon disease/disorder related to previous quinolone treatment (see **CONTRAINDICATIONS**).

Myasthenia Gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use (including LEVOFLOXACIN) in persons with myasthenia gravis. Avoid phl-LEVOFLOXACIN in patients with a known history of myasthenia gravis (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Neurologic

CNS and Psychiatric Effects

Convulsions, toxic psychoses and increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving quinolones, including levofloxacin. Quinolones including levofloxacin, may also cause 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 **DRUG INTERACTIONS** and **ADVERSE REACTIONS**).

Peripheral Neuropathy
Rare cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation in order to prevent the development of an irreversible condition.

Renal
Safety and efficacy of levofloxacin in patients with impaired renal function (creatinine clearance 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, Recommended Dose and Dosage Adjustment,** Patients with Impaired Renal Function and ***Product Monograph Part II*: DETAILED PHARMACOLOGY, Factors Influencing the Pharmacokinetics,** Special Populations, **Renal Insufficiency**).

Skin
Phototoxicity
Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight or ultraviolet (UV) light while receiving drugs in this class. Excessive exposure to sunlight or UV light 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.

Special Populations
The safety and efficacy of levofloxacin tablets in children, adolescents (under the age of 18 years), pregnant women, and nursing mothers have not been established.

Pregnant Women: 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 ***Product Monograph Part II*: TOXICOLOGY**).

Nursing Women: 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 ***Product Monograph Part II*: TOXICOLOGY**).

Pediatrics (< 18 years of age): Levofloxacin is not indicated for the treatment of patients younger than 18 years of age. Quinolones, including levofloxacin, cause arthropathy in juvenile animals of several species (see ***Product Monograph Part II:* TOXICOLOGY**). The incidence of protocol-defined musculoskeletal disorders in a prospective long-term surveillance study was higher in children treated for approximately 10 days with levofloxacin than in children treated with non-fluoroquinolone antibiotics for approximately 10 days (see **ADVERSE REACTIONS**).

Geriatrics (≥ 65 years of age): 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.

Elderly patients may be more susceptible to drug-associated effects on the QT interval (See **WARNINGS AND PRECAUTIONS, Cardiovascular**).

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as phl-LEVOFLOXACIN. This risk is further increased in patients receiving concomitant corticosteroid therapy (see **WARNINGS AND PRECAUTIONS**, **Musculoskeletal**).

Severe and sometimes fatal cases of hepatotoxicity have been reported post-marketing in association with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity (see **WARNINGS AND PRECAUTIONS**, **Hepatic**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In North American Phase III clinical trials involving 7537 subjects, the incidence of treatment-emergent adverse events in patients treated with Levofloxacin Tablets was comparable to comparators. The majority of adverse events were considered to be mild to moderate, with 5.6% of patients considered to have severe adverse events. Among patients receiving multiple-dose therapy, 4.2% discontinued therapy with levofloxacin due to adverse experiences. The incidence of drug-related adverse reactions was 6.7%.

In clinical trials, the most frequently reported adverse drug reaction occurring in > 3% of the study population were nausea, headache, diarrhea, insomnia, dizziness and constipation.

Serious and otherwise important adverse drug reactions are discussed in greater detail in other sections (see **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The data described below reflect exposure to levofloxacin in 7537 patients in 29 pooled Phase III clinical trials. The population studied had a mean age of 49.6 years (74.2% of the population was < 65 years), 50.1% were male, 71.0% were Caucasian, 18.8% were Black. Patients were treated with levofloxacin for a wide variety of infectious diseases (See **INDICATIONS AND CLINICAL USE**). Treatment duration was usually 3-14 days, the mean number of days on therapy was 9.6 days and the mean number of doses was 10.2. Patients received levofloxacin doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. The overall incidence, type and distribution of adverse reactions was similar in patients receiving levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily.

Adverse reactions (characterized as likely related to drug-therapy) occurring in ≥ 1% of levofloxacin -treated patients is shown in Table 1.1 below.

Table 1.1: Common (≥1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin

System/Organ Class	Adverse Reaction	% (N=7537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia	4[a]
Nervous System Disorders	headache dizziness	6 3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea	1
Gastrointestinal Disorders	nausea diarrhea constipation abdominal pain vomiting dyspepsia	7 5 3 2 2 2
Skin and Subcutaneous Tissue Disorders	rash pruritus	2 1
Reproductive System and Breast Disorders	vaginitis	1[b]
General Disorders and Administration Site Conditions	edema injection site reaction chest pain	1 1 1
[a] N = 7274 [b] N=3758 (women)		

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

Less common adverse reactions occurring in 0.1 to < 1% of levofloxacin treated patients is shown in Table 1.2 below.

Table 1.2: Less Common (0.1 to <1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin

System/Organ Class	Adverse Reaction
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia, thrombocytopenia, granulocytopenia
Immune System Disorders	allergic reaction
Metabolism and Nutrition Disorders	hyperglycemia, hypoglycemia, hyperkalemia
Psychiatric Disorders	anxiety, agitation, confusion, depression, hallucination, nightmare[a], sleep disorder[a], anorexia, abnormal dreaming[a]
Nervous System Disorders	tremor, convulsions, paresthesia, vertigo, hypertonia, hyperkinesias, abnormal gait, somnolence[a], syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest, palpitation, ventricular tachycardia, ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis, stomatitis, pancreatitis, oesophagitis, gastroenteritis, glossitis, pseudomembranous/*C.difficile* colitis
Hepatobiliary Disorders	abnormal hepatic function, increased hepatic enzymes, increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	urticaria
Musculoskeletal and Connective Tissue Disorders	tendinitis, arthralgia, myalgia, skeletal pain
Renal and Urinary Disorders	abnormal renal function, acute renal failure

[a] N=7274

Rare (< 0.1%) adverse reactions from Phase III studies include dyspnea and rash maculo-papular.

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.

Abnormal Hematologic and Clinical Chemistry Findings

Laboratory abnormalities seen in > 2% of patients receiving multiple doses of levofloxacin: decreased glucose 2.1%

It is not known whether this abnormality was caused by the drug or the underlying condition being treated.

Pediatric Data

In a group of 1534 pediatric patients (6 months to 16 years of age) treated with levofloxacin for respiratory infections, children 6 months to 5 years of age received 10 mg/kg of levofloxacin twice a day for approximately 10 days and children greater than 5 years of age received 10 mg/kg to a maximum of 500 mg of levofloxacin once a day for approximately 10 days. The adverse reaction profile was similar to that reported in adult patients. Vomiting and diarrhea were reported more frequently in children than reported in adults. However, the frequency of vomiting and diarrhea was similar in levofloxacin-treated and non-fluoroquinolone antibiotic comparator-treated children.

A subset of 1340 of these children treated with levofloxacin for approximately 10 days was enrolled in a prospective, long-term, surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendonopathy, gait abnormality) during 60 days and 1 year following the first dose of levofloxacin.

During the 60-day period following the first dose, the incidence of protocol-defined musculoskeletal disorders was greater in levofloxacin-treated children than in non- fluoroquinolone antibiotic comparator-treated children (2.1% vs. 0.9%, respectively [p=0.038]). In 22/28 (78%) of these children, reported disorders were characterized as arthralgia. A similar observation was made during the 1-year period, with a greater incidence of protocol-defined musculoskeletal disorders in levofloxacin-treated children than in non-fluoroquinolone antibiotic comparator-treated children (3.4% vs. 1.8%, respectively [p=0.025]). The majority of these disorders occurring in children treated with levofloxacin were mild and resolved within 7 days. Disorders were moderate in 8 children and mild in 35 (76%) children.

Post-Market Adverse Drug Reactions

Table 1.3 lists adverse reactions that have been identified during post-approval use of levofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 1.3: Post-Marketing Reports of Adverse Drug Reactions

System Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	pancytopenia, aplastic anemia, leucopenia, hemolytic anemia, eosinophilia, thrombocytopenia including thrombotic thrombocytopenic purpura, agranulocytosis
Immune System Disorders	hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions, anaphylactic shock, angioneurotic edema, serum sickness
Psychiatric Disorders	psychosis, paranoia, isolated reports of suicide attempt and suicidal ideation
Nervous System Disorders	anosmia, ageusia, parosmia, dysgeusia, peripheral neuropathy, isolated reports of encephalopathy, abnormal EEG, dysphonia, exacerbation of myasthenia gravis, amnesia, pseudotumor cerebri
Eye Disorders	vision disturbance (including diplopia), visual acuity reduced, vision blurred, scotoma
Ear and Labyrinth Disorders	hypoacusis, tinnitus
Cardiac Disorders	isolated reports of torsade de pointes, electrocardiogram QT prolonged, tachycardia
Vascular Disorders	vasodilation, vasculitis, DIC
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis, interstitial pneumonia, laryngeal edema, apnea
Hepatobiliary Disorders	hepatic failure (including fatal cases), hepatitis, jaundice, hepatic necrosis
Skin and Subcutaneous Tissue Disorders	bullous eruptions to include: Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme, photosensitivity/phototoxicity reaction, leukocytoclastic vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture, muscle injury (including rupture), rhabdomyolysis, myositis, myalgia
Renal and Urinary Disorders	interstitial nephritis, nephrosis, glomerulonephritis
General Disorders and Administration Site Conditions	multi-organ failure, pyrexia, rash
Investigations	prothrombin time prolonged, international normalized ratio (INR) prolonged, muscle enzymes increased (CPK)

DRUG INTERACTIONS

Overview

Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. The P450 system is not involved in the levofloxacin metabolism, and is not affected by levofloxacin. Levofloxacin is unlikely to alter the pharmacokinetics of drugs metabolized by these enzymes. Disturbances of blood glucose have been reported in patients treated concomitantly with levofloxacin and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents, including levofloxacin, are co- administered. As with all other quinolones, iron and antacids significantly reduced bioavailability of levofloxacin.

Drug-Drug Interactions

Table 1.4: Established or Potential Drug-Drug Interactions

Proper name	Ref	Effect	Clinical comment
Antacids, Sucralfate, Metal Cations, Multi-Vitamins	T	Due to the chelation of levofloxacin by multivalent cations, concurrent administration of levofloxacin tablets with antacids containing calcium, magnesium, or aluminum, as well as sucralfate, metal cations such as iron, multivitamin preparations with zinc, or any products containing any of these components may interfere with the gastrointestinal absorption of levofloxacin, 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.
Theophylline	CT/T	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.	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 AND PRECAUTIONS**).
Warfarin	T	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 elderly patients.
Cyclosporine	CT	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 ke were slightly lower, while Tmax and t½ were slightly longer in the presence of cyclosporine, than those observed in other studies without concomitant medication. The differences,	No dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

		however, are not considered to be clinically significant.	
Digoxin	CT	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.	No dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.
Probenecid and Cimetidine	CT	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 (NSAIDs)	T	Although not observed with levofloxacin in clinical trials, some quinolones have been reported to have proconvulsant activity that is exacerbated with concominant use of NSAIDs.	The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures (see **WARNINGS AND PRECAUTIONS; Neurologic** and ***Product Monograph Part II,* DETAILED PHARMACOLOGY, Animal Pharmacology**).
Antidiabetic Agents	C	Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with levofloxacin and an antidiabetic agent. Some of these cases were serious.	Careful monitoring of blood glucose is recommended when these agents, including levofloxacin, are co-administered.
Zidovudine	CT	Levofloxacin absorption and disposition in HIV-infected subjects, with or without concomitant zidovudine treatment, were similar. The effect of levofloxacin on zidovudine pharmacokinetics has not been studied.	No dosage adjustment for levofloxacin appears to be required when co-administered with zidovudine.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug-Food Interactions

Levofloxacin may be taken with or without food.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

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.

DOSAGE AND ADMINISTRATION

Dosing Considerations

The dosage of levofloxacin tablets 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 Patients with Impaired Renal Function subsection.

Recommended Dose and Dosage Adjustment

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
	750 mg****	q24h	5 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
	750 mg‡	q24h	5 days
Acute Pyelonephritis	250 mg	q24h	10 days
	750 mg	q24h	5 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 Levoflaxacin Injection to an equivalent dose of phl-LEVOFLOXACIN 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*.

**** The efficacy of a regimen of 750 mg daily for 5 days has been demonstrated to be non-inferior to a regimen of 500 mg daily for 10 days. The 750 mg daily 5-day regimen has not been compared to a regimen of 500mg daily for 11-14 days.

‡ The efficacy of this alternative regimen has been documented for infections caused by *Escherichia coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis.* Efficacy against infections caused by *Enterococcus faecalis, Enterobacter cloacae*, or *Pseudomonas aeruginosa* has not been demonstrated with this regimen.

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 **WARNINGS AND PRECAUTIONS, Renal; ACTION AND CLINICAL**

PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency and *Product Monograph Part II*: DETAILED PHARMACOLOGY, Factors Influencing the Pharmacokinetics, Special Populations**, Renal Insufficiency**).

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 modelling 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/Acute Sinusitis/Complicated UTI/Acute Pyelonephritis		
ClCr 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)

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

Women: 0.85 × the value calculated for men.

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

Missed Dose
More than the prescribed dose of phl-LEVOFLOXACIN should not be taken, even if a dose is missed.

Administration
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.

OVERDOSAGE

In the event of an acute overdosage, activated charcoal may be administered to aid in the removal of unabsorbed drug. General supportive measures are recommended. The patient should be observed, including ECG monitoring (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics,** Studies Measuring Effects on QT and Corrected QT (QTc) Intervals), and appropriate hydration maintained. Treatment should be supportive. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
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.

Pharmacodynamics

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, 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 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 (see ***Product Monograph Part II*: DETAILED PHARMACOLOGY, Human Pharmacology, Studies Measuring the Effects on QT and Corrected QT (QTc) Intervals**).

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 Table 1.5.

Table 1.5: Summary of Pharmacokinetic Parameters (mean ± SD)

Regimen	N	Cmax (µg/mL)	Tmax (h)	AUCj (µg□h/mL)	CL/F (mL/min)	Vd/F (L)	t1/2 (h)	Clr (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 ± 1.2b	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 ± 6.7x	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg q24h i.v.[a]	10	6.4 ± 0.8	ND	54.6 ± 11.1x	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 ± 4.0i	ND	72.5 ± 51.2i,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 ± 0.91b	ND	72.5 ± 0.8x	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/mink	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/mink	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

Absorption:

Oral

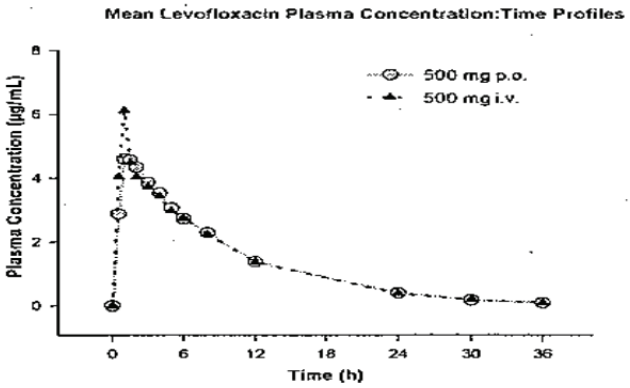
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1 to 2 hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin is approximately 99% in both cases, demonstrating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

Special Populations and Conditions
Pediatrics: The pharmacokinetics of levofloxacin in pediatric patients have not been studied.

Geriatrics: 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.

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.

Race: The apparent total body clearance and apparent volume of distribution were not affected by race in a covariate analysis performed on data from 72 subjects.

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.

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 Table 1.5. 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 modelling 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 **WARNINGS AND PRECAUTIONS; Renal**, and **DOSAGE AND ADMINISTRATION; Recommended Dose and Dosage Adjustment,** 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.

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

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets

250 mg : Each pink, modified rectangular-shaped, coated tablet, debossed with "P" logo on one side and "250" on the other side contains the following non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Crospovidone, Iron Oxide Red, polyethylene glycol, Magnesium Stearate, Microcrystalline Cellulose, Polyvinyl, Talc, Titanium Dioxide. Available in bottles of 50 and 100 tablets

500 mg : Each peach, modified rectangular-shaped, coated tablet, debossed with "P" logo on one side and "500" on the other side, contains the following non-medicinal ingredients: Colloidal Silicon Dioxide, Copovidone, Crospovidone, Hypromellose, Iron Oxide Yellow and Iron Oxide Red, polyethylene glycol, Magnesium Stearate, Microcrystalline Cellulose, Polydextrose, Titanium Dioxide, Triacetin/Glycerol Triacetate. Available in bottles of 50 and 100 tablets

750 mg: Each white modified rectangular-shaped, coated tablet, debossed with "P" logo on one side and "750" on the other side, contains the following non-medicinal ingredients: Colloidal silicon dioxide, Copovidone, Crospovidone, polyethylene glycol, Magnesium stearate, Microcrystalline cellulose, Polyvinyl Alcohol, Talc, Titanium Dioxide. Available in bottles of 30 and 100 tablets.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

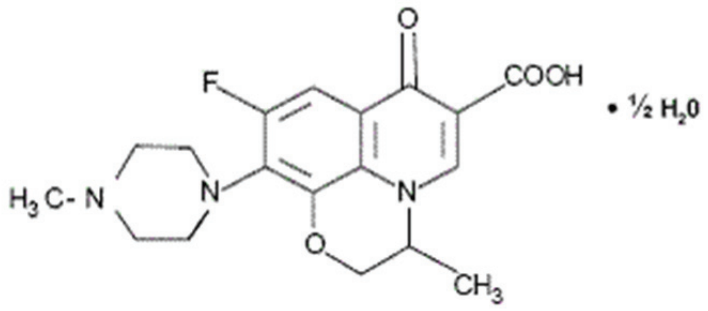
Proper name: levofloxacin

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

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

Molecular mass: 370.38 g/mol

Structural formula:



Physicochemical Properties:

Levofloxacin is a light yellowish white to yellow-white crystal or crystalline powder with a melting point of 226-227°C. The pKa values for levofloxacin are 5.33 and 8.07 for pKa1 and pKa2, 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: $Al^{+3} > Cu^{+2} > Zn^{+2} > Mg^{+2} > Ca^{+2}$.

CLINICAL TRIALS

Comparative Bioavailability Studies

Single dose crossover comparative bioavailability study of phl-LEVOFLOXACIN 500 mg Tablets, was performed versus Janssen-Ortho Inc.'s, LEVAQUIN administered as 1 x 500 mg Tablet in healthy male volunteers / Fasting State. The number of subjects that participated in the study is 22. Bioavailability data were measured and the results are summarized in the following table:

Levofloxacin (1 x 500 mg) From measured data **Uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	phl-LEVOFLOXACIN	LEVAQUIN*	% Ratio of Geometric Means	Confidence Interval (90%)
AUC_T ($\mu g \cdot h/mL$)	32.530 33.051 (17.1)	31.187 31.773 (16.4)	104.31	100.70-108.04
AUC_I ($\mu g \cdot h/mL$)	34.601 35.086 (16.1)	33.239 33.756 (15.3)	104.10	100.49-107.84
C_{max} ($\mu g/mL$)	3.738 3.793 (22.1)	3.599 3.700 (22.3)	103.86	97.73-110.39
T_{max}[§] (h)	1.00 (0.50-4.00)	1.33 (0.75-3.00)		
$T_{½}$[€] (h)	7.32 (18.6)	7.14 (18.8)		

[§] Expressed as median (range) only.
[€] Expressed as the arithmetic mean (CV%) only
* LEVAQUIN is manufactured by Janssen-Ortho Inc. and purchased in Canada.

Acute Sinusitis

Study demographics and trial design

Table 2.1 - Summary of patient demographics for clinical trials in Acute Sinusitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)[a]	Mean age (Range)	Gender Male/female
CAPSS-232	Double-blind, randomized, prospective, multicentre	oral levofloxacin 750 mg once daily for 5 days	n=389[b]	41.7 (18-86)	152/237
		oral levofloxacin 500 mg once daily for 10 days	n=391[b]	42.2 (18-85)	173/218
M92-040	Randomized, open-label, active-controlled	oral levofloxacin 500 mg once daily for 10-14 days	n=306	39.2 (18-85)	115/191
		oral amoxicillin 500 mg/clavulanate 125 mg three times daily for 10-14 days	n=309	38.6 (18-84)	110/199
N93-006	Open-label, non-comparative	oral levofloxacin 500 mg once daily for 10-14 days	n=329	41.6 (18-89)	137/192

[a] Subjects enrolled and randomized to treatment
[b] 780 outpatient adults with clinically and radiologically determined acute maxillary sinusitis (ITT population)

Study Results

5 Day Treatment Regimen

Table 2.2 - Results of study CAPSS-232 in Acute Sinusitis

Endpoints	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval[c]
Clinical Success Rate[a,b]	81/90 (90.0) (45.6% cured; 44.4% improved)	89/95 (93.7) (55.8% cured; 37.9% improved)	(-4.8, 12.1)
Microbiologic Eradication Rate[d]	140/152 (92.1)	133/149 (89.3)	(-9.7, 4.1)

[a] Test-of-Cure visit 17 to 22 days after first dose of active study drug (7-12 days after last dose for 500 mg arm, 12-17 days after last dose for 750 mg arm) in microbiologically clinically evaluable population (subset of 462 patients where sinus samples were taken by sinus puncture).
[b] Clinical success was defined as complete (cured) or partial (improved) resolution of pre-treatment signs and symptoms of ABS to such extent that no further antibiotic treatment was deemed necessary
[c] Two-sided 95% CIs (with continuity correction) around the difference in response rates
[d] Microbiologically evaluable population

Table 2.3 - Clinical Success Rates[a] for Microbiologically Evaluable Population[b] (CAPSS-232)

Pathogen	Levofloxacin 750 mg x 5 days n/N (%)		Comparator n/N (%)	
Streptococcus pneumoniae	25/27	(92.6)	26/27	(96.3)
Haemophilus influenzae	19/21	(90.5)	25/27	(92.6)
Moraxella catarrhalis	10/11	(90.9)	13/13	(100.0)

[a] Eradication rate for the three pathogens was the same as clinical success rate because microbiological success was presumed based on clinical success
[b] Subset of 462 patients where sinus samples were taken by sinus puncture

10-14 Day Treatment Regimen

Table 2.4 – Clinical Success[a] in Pivotal Acute Sinusitis Studies – Clinically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
M92-040	236/267 (88.4)	234/268 (87.3)	(-6.8, 4.6)
N93-006	265/300 (88.3)	N/A	N/A

[a] cured plus improved

Table 2.5 – Microbiologic Eradication in Pivotal Acute Sinusitis Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
M92-040	N/A	N/A	N/A
N93-006	127/138 (92.0)	N/A	N/A

Table 2.6 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (N93-006)

Pathogen	Levofloxacin n/N (%)
Haemophilus influenzae	35/36 (97.2)
Streptococcus pneumoniae	32/32 (100.0)
Staphylococcus aureus	31/33 (93.9)
Moraxella (Branhamella) catarrhalis	14/15 (93.3)

Community Acquired Pneumonia

Study demographics and trial design

Table 2.7 - Summary of patient demographics for clinical trials in Community Acquired Pneumonia

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)[a]	Mean age (Range)	Gender Male/female
CAPSS-150	Double-blind, randomized, prospective, multicentre	oral or i.v. levofloxacin 750 mg once daily for 5 days	n=256[b]	53.1 (18-86)	148/108
		oral or i.v. levofloxacin 500 mg once daily for 10 days	n=272[b]	55.3 (18-89)	162/110
K90-071	Open-label, randomized, active-controlled	levofloxacin oral 488 mg or i.v. 500 mg once daily for 7-14 days	n=295	49.0 (18-87)	162/133
		oral cefuroxime axetil 500 mg twice daily or i.v. ceftriaxone sodium 1 to 2 g once daily or in equally divided doses given twice daily for 7-14 days	n=295	50.3 (18-96)	163/132
M92-075	Open-label, non-comparative	oral or i.v. levofloxacin 500 mg once daily for 7-14 days	n=264	51.9 (18-93)	146/118

[a] Subjects enrolled and randomized to treatment
[b] 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia

Study Results

5 Day Treatment Regimen

Table 2.8 - Results of study CAPSS-150 in Community Acquired Pneumonia

Endpoints	levofloxacin 750 mg once daily for 5 days n/N (%)	Comparator n/N (%)	95% Confidence Interval[c]
Clinical Success Rate[a,b]	183/198 (92.4)	175/192 (91.1)	(-7.0, 4.4)
Microbiologic Eradication Rate[d]	96/103 (93.2)	85/92 (92.4)	(-8.6, 7.0)

[a] 7-14 days after last dose of active study medication for clinically evaluable population
[b] success rates include the clinical response category of cured and improved
[c] two-sided 95% CIs (with continuity correction) around the difference in response rates
[d] 7-14 days after last dose of active study medication for microbiologically evaluable population

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.

Table 2.9 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (5-day regimen)

Pathogen	Levofloxacin 750 mg n/N (%)
Penicillin susceptible S. *pneumoniae*	19/22 (86.4)
Haemophilus influenzae	12/13 (92.3)
Haemophilus parainfluenzae	12/12 (100.0)
Mycoplasma pneumoniae	32/34 (94.1)
Chlamydia pneumoniae	20/22 (90.9)
Legionella pneumophila	12/12 (100.0)

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 community-acquired pneumonia (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**).

The following tables describe the results from the two pivotal trials for community-acquired pneumonia (7-14 day treatment regimen).

Table 2.10 – Clinical Success[a] in Pivotal Community Acquired Pneumonia Studies – Clinically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-071	218/226 (96.5)	208/230 (90.4)	(-10.7, -1.3)
M92-075	222/234 (94.9)	N/A	N/A

a cured plus improved

Table 2.11 – Microbiologic Eradication in Pivotal Community Acquired Pneumonia Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-071	126/128 (98.4)	126/144 (87.5)	(-17.1, -4.7)
M92-075	155/163 (95.1)	N/A	N/A

Table 2.12 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (K90-071)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Chlamydia pneumoniae	46/47 (97.9)	49/53 (92.5)
Streptococcus pneumoniae	39/39 (100.0)	39/40 (97.5)
Haemophilus influenzae	30/30 (100.0)	19/24 (79.2)
Mycoplasma pneumoniae	19/19 (100.0)	22/22 (100.0)
Staphylococcus aureus	10/10 (100.0)	9/9 (100.0)
Haemophilus parainfluenzae	7/8 (87.5)	15/21 (71.4)
Moraxella (Branhamella) catarrhalis	7/7 (100.0)	6/7 (85.7)
Legionella pneumophila	5/5 (100.0)	3/4 (75.0)
Klebsiella pneumonia	3/3 (100.0)	8/8 (100.0)

Table 2.13 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (M92-075)

Pathogen	Levofloxacin n/N (%)
Chlamydia pneumoniae	71/75 (94.7)
Streptococcus pneumoniae	43/44 (97.7)
Haemophilus influenzae	38/39 (97.4)
Staphylococcus aureus	10/12 (83.3)
Moraxella (Branhamella) catarrhalis	11/11 (100.0)
Mycoplasma pneumoniae	10/10 (100.0)
Haemophilus parainfluenzae	8/9 (88.9)
Klebsiella pneumonia	7/7 (100.0)
Legionella pneumophila	4/5 (80.0)

Acute Bacterial Exacerbation of Chronic Bronchitis

Study demographics and trial design

Table 2.14 - Summary of patient demographics for clinical trials in Acute Bacterial Exacerbation of Chronic Bronchitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)[a]	Mean age (Range)	Gender male/female
CAPSS-197	Multicentre randomized, blinded, non-inferiority	oral levofloxacin 750 mg once daily for 5 days	n=187b	58 (18-91)	93/94
		oral amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days	n=182b	59 (20-85)	88/94
K90-070	Open-label, randomized, active-controlled	oral levofloxacin 488 mg once daily for 5-7 days	n=187	59.8 (21-89)	107/80
		oral cefaclor 250 mg three times daily for 7-10 days	n=186	61.2 (19-89)	108/78
M92-024	Open-label, randomized, active-controlled	oral levofloxacin 500 mg once daily for 5-7 days	n=248	51.7 (18-97)	124/124
		oral cefuroxime axetil 250 mg twice daily for 10 days	n=244	53.1 (18-87)	140/104

a Subjects enrolled and randomized to treatment

b From ITT population. Study subjects were characterized by FEV1<50% predicted, or FEV1 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

5 Day Treatment Regimen

Table 2.15 - Results of Study CAPSS-197 in Acute Bacterial Exacerbation of Chronic Bronchitis

Endpoints	Levofloxacin 750 mg once daily for 5 days n/N (%)	Comparator n/N (%)	Difference[c]	95% Confidence Interval[d]
Clinical Success Rate[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)
Microbiologic Eradication Rate[e]	70/86 (81.4)	71/89 (79.8)	-1.6	(-13.9, 10.7)

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

e Microbiologically evaluable population

Table 2.16 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population

Pathogen	Levofloxacin n/N (%)	Comparator 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)

7 Day Treatment Regimen

Table 2.17 – Clinical Success[a] in Pivotal Acute Bacterial Exacerbation of Chronic Bronchitis Studies – Clinically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-070	141/154 (91.6%)	142/155 (91.6%)	(-6.5, 6.6)
M92-024	210/222 (94.6%)	212/229 (92.6%)	(-6.8, 2.7)

a Cured plus improved

Table 2.18 – Microbiologic Eradication in Pivotal Acute Bacterial Exacerbation of Chronic Bronchitis Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-070	97/103 (94.2)	77/89 (86.5)	(-16.6, 1.3)
M92-024	129/134 (96.3)	137/147 (93.2)	(-8.6, 2.5)

Table 2.19 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (K90-070)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Haemophilus influenzae	21/21 (100.0)	17/24 (70.8)
Moraxella (Branhamella) catarrhalis	18/19 (94.7)	8/8 (100.0)
Haemophilus parainfluenzae	14/15 (93.3)	7/7 (100.0)
Pseudomonas aeruginosa	8/10 (80.0)	11/14 (78.6)
Streptococcus pneumoniae	9/10 (90.0)	6/7 (85.7)
Staphylococcus aureus	8/9 (88.9)	2/3 (66.7)

Table 2.20 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (M92-024)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Haemophilus influenzae	42/44 (95.5)	29/31 (93.5)
Haemophilus parainfluenzae	27/27 (100.0)	30/32 (93.8)
Moraxella (Branhamella) catarrhalis	25/25 (100.0)	29/32 (90.6)
Streptococcus pneumoniae	14/16 (87.5)	10/10 (100.0)
Staphylococcus aureus	10/10 (100.0)	34/35 (97.1)
Pseudomonas aeruginosa	9/10 (90.0)	8/9 (88.9)

Nosocomial Pneumonia

Study demographics and trial design

Table 2.21 - Summary of patient demographics for clinical trials in Nosocomial Pneumonia

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)[a]	Mean age (Range)	Gender Male/female
CAPSS-117	Open-label, randomized, active-controlled multicentre	i.v. levofloxacin 750 mg once daily for ≥ 24 hours with switch to oral levofloxacin 750 mg once daily at investigator discretion (7-15 days total)	n=220	55.8 (19-93)	161/59
		i.v. imipenem/cilastatin 0.5-1 g q6-8h for ≥3 days with switch to oral ciprofloxacin 750 mg q12h at investigator discretion (7-15 days total)	n=218	55.5 (18-93)	154/64

[a] Subjects enrolled and randomized to treatment

Table 2.22 - Results of study CAPSS-117 in Nosocomial Pneumonia

Endpoints	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
Clinical Success Rate[a]	70/118 (59.3%)	70/112 (62.5%)	(-9.9, 16.2)
Microbiologic Eradication Rate[b]	62/93 (66.7%)	57/94 (60.6%)	(-20.3, 8.3)

[a] Success includes Cured and Improved; clinically evaluable population
[b] overall microbiologic eradication rates by subject for microbiologically evaluable population

Table 2.23 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (CAPSS-117)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Staphylococcus aureus	14/21 (66.7)	13/19 (68.4)
Pseudomonas aeruginosa	10/17 (58.8)	5/17 (29.4)
Haemophilus influenzae	13/16 (81.3)	14/15 (93.3)
Escherichia coli	10/12 (83.3)	7/11 (63.6)
Klebsiella pneumoniae	9/11 (81.8)	6/7 (85.7)
Serratia marcescenes	9/11 (81.8)	2/7 (28.6)
Streptococcus pneumoniae	3/4 (75.0)	5/7 (71.4)

Uncomplicated Skin and Skin Structure Infections

Study demographics and trial design

Table 2.24 - Summary of patient demographics for clinical trials in Uncomplicated Skin and Skin Structure Infections

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)[a]	Mean age (Range)	Gender male/female
K90-075	Open-label, randomized, active- controlled	oral levofloxacin 488 mg once daily for 7-10 days	n=231	42.8 (15-85)	124/107
		oral ciprofloxacin HCl 500 mg twice daily for 7-10 days	n=238	45.2 (18-88)	118/120
L91-031	Double-blind, randomized, active- controlled	oral levofloxacin 500 mg once daily for 7 days	n=136	43.0 (16-79)	67/69
		oral ciprofloxacin HCl 500 mg twice daily for 10 days	n=136	44.3 (15-81)	78/58

[a] Subjects enrolled and randomized to treatment

Study Results

Table 2.25 – Clinical Success[a] in Pivotal Uncomplicated Skin and Skin Structure Infection Studies – Clinically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-075	178/182 (97.8)	182/193 (94.3)	(-7.7, 0.7)
L91-031	124/129 (96.1)	116/124 (93.5)	(-8.4, 3.3)

[a] cured plus improved

Table 2.26 – Microbiologic Eradication in Pivotal Uncomplicated Skin and Skin Structure Infection Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
K90-075	153/157 (97.5)	135/152 (88.8)	(-14.5, -2.7)
L91-031	93/100 (93.0)	87/97 (89.7)	(-11.7, 5.1)

Table 2.27 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (K90-075)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Staphylococcus aureus	87/87 (100.0)	76/87 (87.4)
Streptococcus pyogenes	14/14 (100.0)	18/20 (90.0)
Pseudomonas aeruginosa	7/8 (87.5)	10/10 (100.0)

Table 2.28 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population(L91-031)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Staphylococcus aureus	66/70 (94.3)	70/75 (93.3)
Streptococcus pyogenes	17/18 (94.4)	12/13 (92.3)
Pseudomonas aeruginosa	5/5 (100.0)	5/5 (100.0)

Complicated Skin and Skin Structure Infections

Study demographics and trial design

Table 2.29 - Summary of patient demographics for clinical trial in Complicated Skin and Skin Structure Infections

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)[a]	Mean age (Range)	Gender male/female
LOFBIV-SSS-040	Multicentre, open-label, randomized, comparative	oral or i.v. levofloxacin 750 mg once daily for 7-14	n=200	51.9 (18-90)	126/74
		i.v. ticarcillin/clavulanate 3.1 g every 4-6 hours alone or followed by amoxicillin/ clavulanate 875 mg twice daily (7-14 days total)	n=199	49.8 (18-90)	117/82

[a] Subjects enrolled and randomized to treatment

Table 2.30 - Results of study LOFBIV-SSS-040 in Complicated Skin and Skin Structure Infections

Endpoints	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
Clinical Success Rate[a]	116/138 (84.1)	106/132 (80.3)	(-13.3, 5.8)
Microbiologic Eradication Rate[b]	82/98 (83.7)	70/98 (71.4)	(-24.3, -0.2)

a Success includes Cured and Improved; clinically evaluable population
b overall microbiologic eradication rates by subject for microbiologically evaluable population

Table 2.31 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (LOFBIV-SSS-040)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Staphylococcus aureus	50/56 (89.3)	35/49 (71.4)
Streptococcus faecalis	8/10 (80.0)	6/11 (54.5)
Streptococcus pyogenes	5/6 (83.3)	6/7 (85.7)
Proteus mirabilis	9/10 (90.0)	7/12 (58.3)
Streptococcus agalactiae	9/12 (75.0)	9/13 (69.2)
Pseudomonas aeruginosa	4/7 (57.1)	5/6 (83.3)

Complicated Urinary Tract Infection and Acute Pyelonephritis

Study demographics and trial design

Table 2.32 - Summary of patient demographics for clinical trials in Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)[a]	Mean age (Range)	Gender male/female
CAPSS-349	Multicentre, randomized, double-blind	i.v. levofloxacin 750 mg and /or oral levofloxacin 750 mg once daily for 5 days	n=537[b]	54.0 (18-94)	207/330
		i.v. ciprofloxacin 400 mg and/or oral ciprofloxacin 500 mg twice daily for 10 days	n=556[b]	54.4 (18-93)	220/336
L91-058	Double-blind, randomized, active-controlled	oral levofloxacin 250 mg once daily for 10 days	n=285	51.7 (18-95)	117/168
		oral ciprofloxacin 500 mg twice daily for 10 days	n=282	49.7 (18-93)	112/170
L91-059	Open-label, randomized, active-controlled	oral levofloxacin 250 mg once daily for 7-10 days	n=326	62.5 (19-92)	124/202
		oral lomefloxacin HCl 400 mg once-daily for 14 days	n=324	59.9 (18-91)	105/219

[a] Subjects enrolled and randomized to treatment

[b] Intent-to-treat population. Patients with AP complicated by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were excluded.

Study results

5 Day Treatment Regimen

Table 2.33 – Clinical Success[a] in Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP) – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval[b]
CAPSS-349	229/265 (86.4)	213/241 (88.4)	(-3.8, 7.7)

a Clinical success includes subjects who were cured or improved at the Posttherapy Visit

b Two-sided 95% confidence interval around the difference (comparator minus levofloxacin).

Table 2.34 - Results of Study CAPSS-349 in Complicated Urinary Tract Infection (cUTI) and Acute Pyelonephritis (AP)

Primary Endpoint	Diagnosis	levofloxacin 750 mg once daily for 5 days	Comparator	Difference[f]	95% Confidence Interval[g]
Microbiologic Eradication[a]	**mITT Population [b,c]**				
	Overall (cUTI or AP)	240/317 (75.7)	229/302 (75.8)	0.1	(-6.6, 6.9)
	cUTI	162/223 (72.6)	151/204 (74.0)	1.4	(-7.0, 9.8)
	AP	78/94 (83.0)	78/98 (79.6)	-3.4	(-14.4, 7.6)
	Microbiologically Evaluable Population [d,e]				
	Overall (cUTI or AP)	228/265 (86.0%)	215/241 (89.2%)	3.2	(-2.5, 8.9)
	cUTI	154/185 (83.2%)	144/165 (87.3%)	4.0	(-3.4, 11.4)
	AP	74/80 (92.5%)	71/76 (93.4%)	0.9	(-7.1, 8.9)

[a] At posttherapy visit (10-14 days after last active dose of levofloxacin and 5-9 days after last active dose of ciprofloxacin).

[b] The mITT population included patients who had a clinical diagnosis of AP or cUTI and who had a positive (≥ 105 CFU/mL) urine culture with no more than 2 uropathogens at Study Entry.

[c] In the mITT population there were a limited number of patients treated with IV therapy (levofloxacin-8, comparator-9), with catheters (levofloxacin-4, comparator-5) and with bacteremia (levofloxacin-13, comparator-12).

[d] The microbiologically evaluable population included patients with a confirmed diagnosis of cUTI or AP according to the protocol- specified inclusion criteria and with a known uropathogen with adequate growth (≥ 105 CFU/mL) who met all other microbiologic evaluability criteria.

[e] In the microbiologically evaluable population there were a limited number of patients treated with IV therapy (levofloxacin-4, comparator-3), with catheters (levofloxacin-3, comparator-3) and with bacteremia (levofloxacin-10, comparator-8).

[f] Difference in eradication rates (comparator minus levofloxacin)

[g] Two-sided 95% confidence interval around the difference (comparator minus levofloxacin) in microbiologic eradication rates.

Table 2.35 - Microbiologic Eradication Rates by Pathogen at Posttherapy Visit

Pathogen	***Levofloxacin 750 mg x 5 days n/N (%)***			***Comparator n/N (%)***		
mITT Population						
	Overall	**AP**	**cUTI**	**Overall**	**AP**	**cUTI**
Escherichia coli	165/206 (80.1)	67/81 (82.7)	98/125 (78.4)	158/216 (73.1)	70/89 (78.7)	88/127 (69.3)
Klebsiella pneumoniae	21/29 (72.4)		19/26 (73.1)	26/29 (89.7)		22/25 (88.0)
Proteus mirabilis	13/13 (100.0)		10/10 (100.0)	6/7 (85.7)		6/7 (85.7)
Escherichia coli with bacteremia		7/12 (58.3)			8/12 (66.7)	
Microbiologically Evaluable Population						
	Overall	**AP**	**cUTI**	**Overall**	**AP**	**cUTI**
Escherichia coli	155/172 (90.1)	63/69 (91.3)	92/103 (89.3)	148/168 (88.1)	63/67 (94.0)	85/101 (84.2)
Klebsiella pneumoniae	20/23 (87.0)		18/21 (85.7)	24/26 (92.3)		21/23 (91.3)
Proteus mirabilis	12/12 (100.0)		9/9 (100.0)	6/6 (100.0)		6/6 (100.0)
Escherichia coli with bacteremia		6/9 (66.7)			7/8 (87.5)	

Table 2.36 - Relapse Rates at Post-Study Visit[a]

	Levofloxacin 750 mg x 5 days n/N (%)	*Comparator n/N (%)*
mITT Population		
Overall (cUTI or AP)	13/207 (6.3)	11/204 (5.4)
cUTI	8/136 (5.9)	10/139 (7.2)
AP	5/71 (7.0)	1/65 (1.5)
Microbiologically Evaluable Population		
Overall (cUTI or AP)	12/199 (6.0)	11/195 (5.6)
cUTI	7/131 (5.3)	10/135 (7.4)
AP	5/68 (7.4)	1/60 (1.7)

[a] 33-40 days after the last active dose of levofloxacin and 28-35 days after the last active dose of ciprofloxacin

10 Day Treatment Regimen

Table 2.37 – Clinical Success[a] in Pivotal cUTI and AP Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
L91-058	163/177 (92.1)	155/171 (90.6)	(-7.6, 4.7)
L91-059	195/209 (93.3)	183/204 (89.7)	(-9.2, 2.0)

[a] cured plus improved

Table 2.38 – Microbiologic Eradication in Pivotal cUTI and AP Studies – Microbiologically Evaluable Subjects

Study Number	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
L91-058	164/177 (92.7)	159/171 (93.0)	(-5.4, 6.0)
L91-059	198/209 (94.7)	189/204 (92.6)	(-7.0, 2.8)

Table 2.39 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (L91-058)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Escherichia coli	88/92 (95.7)	96/99 (97.0)
Klebsiella pneumonia	31/32 (96.9)	22/23 (95.7)
Streptococcus faecalis	8/9 (88.9)	6/11 (54.5)
Proteus mirabilis	13/14 (92.9)	5/5 (100.0)
Pseudomonas aeruginosa	7/12 (58.3)	7/7 (100.0)
Enterobacter cloacae	9/9 (100.0)	4/4 (100.0)

Table 2.40 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (L91-059)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Escherichia coli	118/119 (99.2)	116/118 (98.3)
Klebsiella pneumonia	29/31 (93.5)	23/25 (92.0)
Proteus mirabilis	11/11 (100.0)	9/9 (100.0)
Streptococcus faecalis	4/8 (50.0)	6/8 (75.0)
Pseudomonas aeruginosa	8/9 (88.9)	4/6 (66.7)
Enterobacter cloacae	6/7 (85.7)	4/6 (66.7)

Uncomplicated Urinary Tract Infections

Study demographics and trial design

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Table 2.41 - Summary of patient demographics for clinical trials in Uncomplicated Urinary Tract Infections

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)[a]	Mean age (Range)	Gender Male/female
LOFBO-UTI-060	Double-blind, randomized, active-controlled, multi-centre	oral levofloxacin 250 mg once daily for 3 days	n=298	31.3 (18-57)	0/298
		oral ofloxacin 200 mg twice daily for 3 days	n=296	32.0 (18-71)	0/296

[a] Subjects enrolled and randomized to treatment

Study Results

Table 2.42 - Results of study LOFBO-UTI-060 in Uncomplicated Urinary Tract Infections

Endpoints	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
Clinical Success Rate[a]	154/157 (98.1)	160/165 (97.0)	(-4.8, 2.6)
Microbiologic Eradication Rate[b]	151/157 (96.2)	153/165 (92.7)	(-8.7, 1.8)

[a] Success includes Cured and Improved; microbiologically evaluable population

[b] Overall microbiologic eradication rates by subject for microbiologically evaluable population

Table 2.43 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (LOFBO-UTI-060)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Escherichia coli	125/127 (98.4)	131/138 (94.9)
Klebsiella pneumoniae	10/11 (90.9)	8/8 (100.0)
Staphylococcus saprophyticus	8/8 (100.0)	3/3 (100.0)
Staphylococcus aureus	5/5 (100.0)	3/3 (100.0)

Chronic Bacterial Prostatitis

Study demographics and trial design

Table 2.44 - Summary of patient demographics for clinical trials in Chronic Bacterial Prostatitis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)[a]	Mean age (Range)	Gender Male/female
CAPSS-101	Double-blind, randomized, active-controlled, comparative	oral levofloxacin 500 mg once daily for 28 days	n=197	50.9 (18-81)	197/0
		oral ciprofloxacin 500 mg twice daily for 28 days	n=180	51.5 (19-83)	180/0

[a] Subjects enrolled and randomized to treatment

Study Results

Table 2.45 - Results of study CAPSS-101 in Chronic Bacterial Prostatitis

Endpoints	Levofloxacin n/N (%)	Comparator n/N (%)	95% Confidence Interval
Clinical Success Rate[a]	122/170 (71.8)	107/151 (70.9)	(-11.15, 9.34)
Microbiologic Eradication Rate[b]	102/136 (75.0)	96/125 (76.8)	(-8.98, 12.58)

[a] Success includes Cured and Improved; mITT
[b] Overall microbiologic eradication rates by subject for microbiologically evaluable population

Table 2.46 - Microbiologic Eradication Rates by Pathogen for Microbiologically Evaluable Population (CAPSS-101)

Pathogen	Levofloxacin n/N (%)	Comparator n/N (%)
Escherichia coli	14/15 (93.3)	9/11 (81.8)
Enterococcus faecalis	39/54 (72.2)	34/45 (75.6)
Staphylococcus epidermis	20/24 (83.3)	26/29 (89.7)

DETAILED PHARMACOLOGY

Animal Pharmacology

Pharmacodynamics

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

Table 2.47 - 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

System	Species	Major Findings
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 rat	At 200 mg/kg, i.v., inhibition of gastric propulsion ≥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 Muscle		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

Pharmacodynamics

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 C_{max} 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)

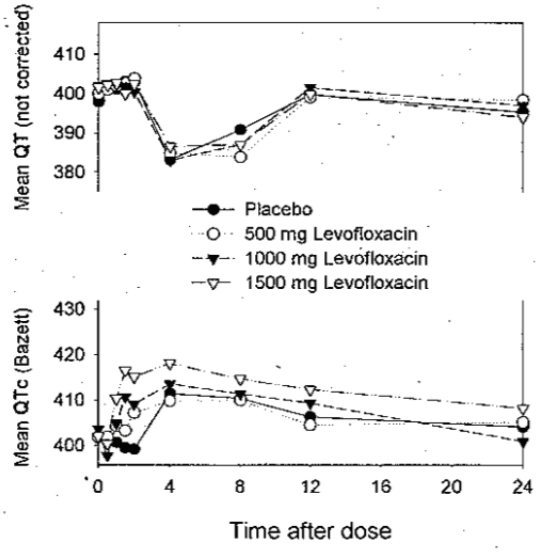
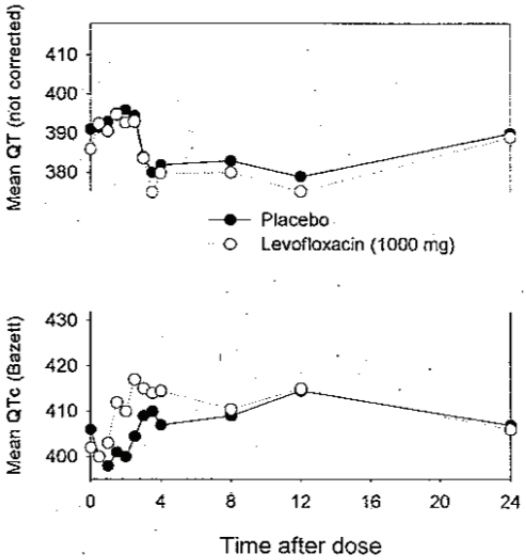


FIGURE B
Mean QT and QTc Bazett versus Time after Dose of Placebo or 1000 mg of Levofloxacin (Comparative Study n=48)



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 (mg)	n	Peak Plasma Concentration (ug/mL)	Area Under the Curve $AUC_{0-\omega}$ 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 □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**; **WARNINGS AND 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 ql2h	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
0-6h	185±61.7	98.1 ±48.1	66.5±27.3
6-12h	91.6 ± 24.4	75.2 ± 22.1	39.0 ± 23.1
12-24h	156 ± 183	58.6 ± 31.1	29.5 ± 20.7
24-36h	49.7±16.2	44.1±10.6	<25
36-48h	<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 pyelonephritisa:

Collection Interval	Cl_{cr} 50-80 mL/min	Cl_{cr} 20-49 mL/min	Cl_{cr} < 20 mL/min
	receiving 250 mg	receiving 250 mg	receiving 250 mg
	q24h	q24h	q48h
0-6h	161	103	54
6-12h	61	76	29
12-24h	40	58	24
24-36h	--	--	23
36-48h	--	--	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 CI_{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 CD_4 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 **DRUG INTERACTIONS**).

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 Table 2.48.

Table 2.48- 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 coii	(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

Organism	(# of isolates)	MIC (µg /mL)			
		50%	90%	Range	
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
Serratia spp.	(65)	0.120	0.500	0.030-	>16.000
Serratia marcescents	(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
Staphyloccus 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
Strptococcus (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 (MIÇ0.06µg/mL)[‡]	(2699)	0.500	1.000	0.004-	>8.000
Streptococcus pneumoniae, penicillin-resistant (MIÇ2.0µg/mL)[‡]	(538)	0.500	1.000	0.004-	2.000
Streptococcus pneumoniae, clarithromycin-susceptible (MIÇ0.25µg/mL)[‡]	(502)	0.500	1.000	0.250-	>16.000
Streptococcus pneumoniae, clarithromycin-resistant (MIÇ1.0µg/mL)[‡]	(136)	1.000	2.000	0.12-	16.000
Streptococcus pneumoniae, erythromycin-resistant (MIÇ1.0µg/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 AND PRECAUTIONS; 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 microorganisms 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 *Nisseria 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% CO2.

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2. National Committee for Clinical Laboratory Standards: Performance Standards for Antimicrobial Disk Susceptibility Tests, Sixth Edition, 1997.

TOXICOLOGY

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

Acute Toxicity

Table 2.49- Summary of the acute toxicity studies

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

Table 2.50 - Summary of the sub-chronic toxicity studies

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

Species, Age/Grp/No., Sex/Grp	Route, Dosage, Duration	Results
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

Species, Age/Grp/No., Sex/Grp	Route, Dosage, Duration	Results
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
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

Table 2.51 - Segment I: Fertility and Reproductive Performance Studies

Study[a]	Parental Toxicity	Embryo/Fetal Toxicity	Teratogenicity
Oral gavage, rat 0, 10, 60, 360 mg/kg/da y 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/da y 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.

Table 2.52 - 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

Table 2.53 - 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 AND PRECAUTIONS**). 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).

Three-month old beagle dogs dosed orally with up to 40 mg/kg/day levofloxacin for 8 or 9 consecutive days, with an 18-week recovery period, exhibited musculoskeletal clinical signs by the final dose at dose levels ≥2.5 mg/kg (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (equivalent to and 3-fold greater than the potential therapeutic dose, respectively). All musculoskeletal clinical signs were resolved by week 5 of recovery; synovitis was resolved by the end of the 18-week recovery period; whereas, articular cartilage erosions and chondropathy persisted.

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 IC50 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 to 100 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 (MAP90) was not significantly affected by levofloxacin 0.3 and 3.0 mg/kg IV.

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PART III: CONSUMER INFORMATION

Pr phl-LEVOFLOXACIN
Levofloxacin Tablets (as Levofloxacin Hemihydrate)

This leaflet is part III of a three-part "Product Monograph" published when phl-LEVOFLOXACIN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about phl-LEVOFLOXACIN. Contact your doctor or pharmacist if you have any questions about the drug.

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.

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

ABOUT THIS MEDICATION

What the medication is used for:
phl-LEVOFLOXACIN is from a group of antibiotics known as quinolones. phl-LEVOFLOXACIN is used to treat adults with certain lung, sinus, skin and urinary tract infections caused by certain germs called bacteria.

What it does:
Levofloxacin has been shown, in a large number of clinical trials, to be effective for the treatment of bacterial infections. Levofloxacin interferes with bacterial enzymes to prevent bacterial growth, thereby killing many 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). phl-LEVOFLOXACIN tablets, like other antibiotics, does not kill viruses.

When it should not be used:
You should not take phl-LEVOFLOXACIN if you have had an allergic reaction to any of the group of antibiotics known as quinolones, or to any of the nonmedicinal ingredients (see **What the nonmedicinal ingredients are**). This includes antibiotics such as ofloxacin, ciprofloxacin, moxifloxacin hydrochloride, gatifloxacin and norfloxacin. If you have had any reaction to quinolones, you should discuss this with your doctor.

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

What the medicinal ingredient is:
Levofloxacin

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, copovidone, crospovidone, polyethylene glycol, magnesium stearate, microcrystalline cellulose and titanium dioxide. In addition, the 250 mg tablets also contain iron oxide red and polyvinyl alcohol-part hydrolyzed, talc. The 500 mg tablets contain iron oxide yellow and red, polydextrose and triacetin. The 750 mg tablets contain polyvinyl alcohol (part. hydrolyzed), talc.

What dosage forms it comes in:
Tablets: 250 mg, 500 mg, 750 mg

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Levofloxacin has been shown to lengthen the heartbeat on an electrocardiogram test (QT interval prolongation).
- Serious hypersensitivity (allergic) reactions, sometimes fatal, have been reported in some patients receiving quinolone therapy, including levofloxacin.
- Seizures may occur with quinolone therapy. Tell your doctor if you have any central nervous system problems (ie, epilepsy). Your doctor will determine whether you should use this medication.
- Fluoroquinolines, including phl-LEVOFLOXACIN may worsen muscle weakness in person with myasthenia gravis. **Do not use** phl-LEVOFLOXACIN if **you have or have had** myasthenia gravis.
- Fluoroquinolines, including phl-LEVOFLOXACIN are associated with an increased risk of tendinitis and tendon rupture in all ages, This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

See **SIDE EFFECTS AND WHAT TO DO ABOUT THEM.**

BEFORE you use phl-LEVLOFLOXACIN talk to your doctor or pharmacist if:

- You have decreased kidney function.
- You have epilepsy or have a history of seizures (convulsions).
- you have had any problems with your heart rhythm, heart rate, or problems with low potassium.
- you are taking anti-diabetic medications as

phl-LEVOFLOXACIN may interfere with blood sugar levels.
- You you have a disease that causes muscle weakness (myasthenia gravis).
- you experience any symptoms of muscle weakness, including breathing difficulties (e.g., shortness of breath).

INTERACTIONS WITH THIS MEDICATION

Before taking phl-LEVOFLOXACIN 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 phl-LEVOFLOXACIN tablets may react with certain medications.

Taking warfarin and phl-LEVOFLOXACIN tablets together can further predispose you to the development of bleeding problems. If you take warfarin, be sure to tell your doctor.

Many multivitamin /mineral combinations and antacids, containing calcium, magnesium, aluminum, iron, zinc and sucralfate may interfere with the absorption of phl-LEVOFLOXACIN tablets and may prevent it from working properly. You should take phl-LEVOFLOXACIN 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 phl-LEVOFLOXACIN is taken with any of these medications. Do not take any of these medications with phl-LEVOFLOXACIN tablets unless your doctor tells you that it is all right.

*No longer marketed in Canada

PROPER USE OF THIS MEDICATION

Usual Adult dose:
phl-LEVOFLOXACIN tablets should be taken once a day for 3, 5, 7, 10, 14 or 28 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, to maintain a hydrated condition.

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.**

Overdose:

In case of drug overdose, contact a healthcare practitioner (e.g., doctor), hospital emergency department, or regional poison control centre, even if there are no symptoms.

Missed Dose:
Do not take more than the prescribed dose of phl-LEVOFLOXACIN tablets even if you missed a dose by mistake. You should not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

phl-LEVOFLOXACIN is generally well tolerated. The most common side effects caused by phl-LEVOFLOXACIN, which are usually mild, include nausea, vomiting, diarrhea, abdominal pain, constipation, dizziness, flatulence, rash, headache, difficulty in sleeping, and vaginitis in women. However, allergic reactions have been reported in patients receiving quinolones, including levofloxacin 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.

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

Pain, swelling and tears of shoulder, hand, or Achilles tendons have been reported in patients receiving quinolones, including levofloxacin tablets. The risk of tendon effects is higher if you are over 65 years old, and especially if you are taking corticosteroids. If you develop pain, swelling, or rupture of a tendon you should stop taking phl-LEVOFLOXACIN tablets, rest, avoid exercise and strenuous use of the affected area and contact your doctor.

Convulsions have been reported in patients receiving quinolone antibiotics including LEVOFLOXACIN tablets. If you have experienced convulsions in the past, be sure to let your physician know that you have a history of convulsions.

Quinolones, including phl-LEVOFLOXACIN 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. If you have suicidal thoughts contact your doctor.

Neuropathy (problems in the nerves) has been reported in patients receiving quinolones, including levofloxacin tablets. If neuropathy symptoms occur such as pain, burning, tingling, numbness, weakness, or other alterations of sensation (including feelings of vibration, temperature or touch sensitivity), you should stop taking phl-LEVOFLOXACIN tablets and contact your doctor immediately.

Sun sensitivity (photosensitivity), which can appear as skin eruption or severe sunburn, can occur in some patients taking quinolone antibiotics after exposure to sunlight or artificial ultraviolet (UV) light (e.g., tanning beds). Levofloxacin has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking phl-LEVOFLOXACIN. Use sunscreen and wear protective clothing if out in the sun. If photosensitivity develops, contact your doctor.

If you have diabetes and you develop a hypoglycemic reaction (low blood sugar) while taking phl-LEVOFLOXACIN tablets, you should stop taking phl-LEVOFLOXACIN tablets and call your doctor. Hyperglycemic and hypoglycemic (high low blood sugar respectively) reactions have also been reported in patients without diabetes. Common symptoms of hyperglycemia (high blood sugar) include excessive thirst or excessive urination. Common symptoms of hypoglycemia (low blood sugar) include dizziness, excessive hunger, lack of coordination, headache, fatigue, or fainting. You should call your doctor if you experience any of these symptoms.

Problems with the liver, including fatal cases, have been reported in patients taking levofloxacin. The symptoms of hepatic impairment are non-specific and include nausea, vomiting, stomach pain, fever, weakness, abdominal pain or tenderness, loss of appetite, itching, unusual or unexplained tiredness, light coloured bowel movements and dark coloured urine. In more severe cases, these symptoms are followed by jaundice (yellowing of the skin) and/or icterus (yellowing of the eyes). Call your doctor if you experience these symptoms.

Some quinolones have been associated with lengthening of the heartbeat on an electrocardiogram test, and with abnormal heart rhythm. Very rare cases of abnormal heart beat have been reported in patients while on levofloxacin, 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 phl-LEVOFLOXACIN 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.

Diarrhea that usually ends after treatment is a common problem caused by antibiotics. A more serious form of diarrhea can occur during or up to 2 months after the use of antibiotics. This has been reported with all antibiotics including with phl-LEVOFLOXACIN tablets. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your doctor as soon as possible.

Fluoroquinolones like phl-LEVOFLOXACIN tablets may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. If you have or have had myasthenia gravis, do not use phl-LEVOFLOXACIN.

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

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk to your doctor or pharmacist**	**Stop taking drug and seek immediate emergency medical attention**
Rare		
Heart palpitations (fast beating) or fainting spells		✓
Tendon pain, swelling or rupture		✓
Worsening muscle weakness or breathing problems		✓
Symptoms of allergic reaction • skin rash • hives • itching • difficulty breathing or swallowing • swelling of face, tongue or throat		✓
Symptoms of neuropathy • pain • burning • tingling • numbness • weakness		✓
If you have diabetes and you develop a hypoglycemic reaction.		✓
Symptoms of hypoglycemia • dizziness • excessive hunger • lack of coordination • headache • fatigue • fainting	✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM		
Symptom / effect	**Talk to your doctor or pharmacist**	**Stop taking drug and seek immediate emergency medical attention**
Symptoms of hyperglycemia • excessive thirst • excessive urination	✓	
Symptoms of liver problems • yellowing of the skin and/or eyes • nausea • vomiting • loss of appetite • itching	✓	

This is not a complete list of side effects. For any unexpected effects while taking phl-LEVOFLOXACIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15˚C to 30˚ C) in well-closed containers.

Keep out of the reach of children.

Do not use after the expiry date. Generally, all expired medications should be returned to your pharmacist.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll- free at: 866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, ON K1A0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect TM Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effect, please contact your health care provider before notifying Canada Vigilance. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting:
Pharmel Inc.

by telephone: 1-888-550-6060

by post: Pharmel Inc.
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This leaflet was prepared by Pharmel Inc.

Last revised: February 20, 2013