

PRODUCT MONOGRAPH

Pr LEVAQUIN*
levofloxacin

Tablets 250 mg, 500 mg and 750 mg
Injection 5 mg/mL in 5% dextrose

Antibacterial Agent

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Pr **LEVAQUIN***
levofloxacin

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 | None <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i> |
| Intravenous Infusion | Injection 5 mg/mL in 5% dextrose | None <i>For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.</i> |

INDICATIONS AND CLINICAL USE

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

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

Upper Respiratory Tract

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

Lower Respiratory Tract

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

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

CONTRAINDICATIONS

LEVAQUIN levofloxacin Tablets and Injection are contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product. 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

- LEVAQUIN (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 LEVAQUIN (see **WARNINGS AND PRECAUTIONS; Sensitivity/Resistance**).
- Seizures may occur with quinolone therapy. LEVAQUIN 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**).
- LEVAQUIN should not be used in pregnant women unless the potential benefits outweigh the potential risk to the fetus (see **WARNINGS AND PRECAUTIONS; Special Populations**).
- For nursing mothers, a decision should be made to either discontinue nursing or discontinue the administration of LEVAQUIN, taking into account the importance of LEVAQUIN therapy to the mother and the possible risk to the infant (see **WARNINGS AND PRECAUTIONS; Special Populations**).
- LEVAQUIN is not recommended for children under the age of 18 years (see **WARNINGS AND PRECAUTIONS; Special Populations**).

General

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

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

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

Musculoskeletal Effects

Ruptures of the shoulder, hand, Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendonitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin (see **CONTRAINDICATIONS**).

I.V. Administration

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

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 **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 LEVAQUIN. In patients treated with LEVAQUIN, 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 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**).

Neurologic

CNS and Psychiatric Effects

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones including levofloxacin, may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, dizziness, confusion and hallucinations, paranoia, depression, nightmares, insomnia and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. alcohol abuse, certain drug therapies such as NSAIDs and theophylline, renal dysfunction). Levofloxacin should be used with caution in patients with unstable psychiatric illness (see **DRUG INTERACTIONS**, and **ADVERSE REACTIONS**).

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

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 **DETAILED PHARMACOLOGY; 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 LEVAQUIN levofloxacin tablets and injection 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 **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 **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 **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**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In North American Phase 3 clinical trials involving 7537 subjects, the incidence of treatment-emergent adverse events in patients treated with LEVAQUIN levofloxacin Tablets and Injection 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 LEVAQUIN levofloxacin in 7537 patients in 29 pooled Phase 3 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 LEVAQUIN 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 LEVAQUIN 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 LEVAQUIN 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 $\geq 1\%$ of LEVAQUIN-treated patients is shown in Table 1 below.

Table 1. Common ($\geq 1\%$) Adverse Reactions Reported in Clinical Trials with LEVAQUIN

| System/Organ Class | Adverse Reaction | % (N=7537) |
|---|-------------------------|-----------------------|
| Infections and Infestations | moniliasis | 1 |
| Psychiatric Disorders | insomnia | 4 ^a |
| Nervous System Disorders | headache | 6 |
| | dizziness | 3 |
| Respiratory, Thoracic and Mediastinal Disorders | dyspnea | 1 |
| Gastrointestinal Disorders | nausea | 7 |
| | diarrhoea | 5 |
| | constipation | 3 |
| | abdominal pain | 2 |
| | vomiting | 2 |
| | dyspepsia | 2 |
| Skin and Subcutaneous Tissue Disorders | rash | 2 |
| | pruritus | 1 |
| Reproductive System and Breast Disorders | vaginitis | 1 ^b |
| General Disorders and Administration Site Conditions | oedema | 1 |
| | injection site reaction | 1 |
| | chest pain | 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 LEVAQUIN-treated patients is shown in Tables 2 below.

Table 2. Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN

| System/Organ Class | Adverse Reaction |
|--|---|
| Infections and Infestations | genital moniliasis |
| Blood and Lymphatic System Disorders | anaemia, thrombocytopenia, granulocytopenia |
| Immune System Disorders | allergic reaction |
| Metabolism and Nutrition Disorders | hyperglycaemia, hypoglycaemia, hyperkalaemia |
| Psychiatric Disorders | anxiety, agitation, confusion, depression, hallucination, nightmare ^a , sleep disorder ^a , anorexia, abnormal dreaming ^a |
| Nervous System Disorders | tremor, convulsions, parasthaesia, vertigo, hypertonia, hyperkinaesias, 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/ <i>C.difficile</i> colitis |
| Hepatobiliary Disorders | abnormal hepatic function, increased hepatic enzymes, increased alkaline phosphatase |
| Skin and Subcutaneous Tissue Disorders | urticaria |
| Musculoskeletal and Connective Tissue Disorders | tendonitis, arthralgia, myalgia, skeletal pain |
| Renal and Urinary Disorders | abnormal renal function, acute renal failure |

^a N = 7274

Rare (<0.1%) adverse reactions from Phase 3 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% v 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% v 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 3 lists adverse reactions that have been identified during post-approval use of LEVAQUIN 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 3: Postmarketing 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, amnesia |
| 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 4- Established or Potential Drug-Drug Interactions

| Proper name | Ref | Effect | Clinical comment |
|---|------------|--|---|
| Antacids, Sucralfate, Metal Cations, Multi-Vitamins | T | Tablets: Due to the chelation of levofloxacin by multivalent cations, concurrent administration of LEVAQUIN Tablets with antacids containing calcium, magnesium, or aluminum, as well as sucralfate, metal cations such as iron, multi-vitamin preparations with zinc, or any products containing any of these components may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. | These agents should be taken at least 2 hours before or 2 hours after levofloxacin tablet administration. |
| | T | Injection: There are no data concerning an interaction of intravenous quinolones with oral antacids, sucralfate, multi-vitamins, or metal cations. | Levofloxacin should not be co-administered with any solution containing multivalent cations (e.g. magnesium) through the same intravenous line (see DOSAGE AND ADMINISTRATION; 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 the 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 k_e were slightly lower, while T_{max} and $t_{1/2}$ were slightly longer in the presence of cyclosporine, than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. | No dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly |
| 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. |

| | | | |
|---|----|--|--|
| <u>Probenecid and Cimetidine</u> | 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 $t_{1/2}$ of levofloxacin were 27-38% and 30% higher, respectively, while CL/F and Cl, 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. |
| <u>Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)</u> | T | Although not observed with levofloxacin in clinical trials, some quinolones have been reported to have proconvulsant activity that is exacerbated with concomitant 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 DETAILED PHARMACOLOGY; Animal Pharmacology). |
| <u>Antidiabetic Agents</u> | 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. |
| <u>Zidovudine</u> | 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

LEVAQUIN 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 LEVAQUIN levofloxacin Tablets and Injection for patients with normal renal function (i.e. $Cl_{Cr} > 80$ mL/min) is described in the following dosing chart. For patients with

altered renal function (i.e. $Cl_{Cr} \leq 80$ mL/min), see the Patients with Impaired Renal Function subsection. The 250 mg and 500 mg doses of LEVAQUIN Injection should be administered by slow infusion over 60 minutes every 24 hours while the 750 mg dose is administered by slow infusion over 90 minutes every 24 hours.

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 LEVAQUIN Injection to an equivalent dose of LEVAQUIN Tablets.

*** Efficacy of this alternative regimen has only been documented for infections caused by penicillin-susceptible *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*.

**** The efficacy of a regimen of 750mg daily for 5 days has been demonstrated to be non-inferior to a regimen of 500mg daily for 10 days. The 750mg 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 **ACTION AND CLINICAL PHARMACOLOGY, DETAILED**

PHARMACOLOGY; Special Populations, Renal Insufficiency and **WARNINGS AND PRECAUTIONS; Renal).**

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

| Renal Status | Initial Dose | Subsequent Dose |
|---|-------------------------------|------------------------|
| Acute Sinusitis / Acute Bacterial Exacerbation of Chronic Bronchitis / Community Acquired Pneumonia / Uncomplicated SSSI / Chronic Bacterial Prostatitis | | |
| Cl _{Cr} from 50 to 80 mL/min | No dosage adjustment required | |
| Cl _{Cr} from 20 to 49 mL/min | 500 mg | 250 mg q24h |
| Cl _{Cr} from 10 to 19 mL/min | 500 mg | 250 mg q48h |
| Hemodialysis | 500 mg | 250 mg q48h |
| CAPD | 500 mg | 250 mg q48h |
| Complicated UTI / Acute Pyelonephritis | | |
| Cl _{Cr} ≥ 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 | | |
| Cl _{Cr} from 50 to 80 mL/min | No dosage adjustment required | |
| Cl _{Cr} from 20 to 49 mL/min | 750 mg | 750 mg q48h |
| Cl _{Cr} from 10 to 19 mL/min | 750 mg | 500 mg q48h |
| Hemodialysis | 750 mg | 500 mg q48h |
| CAPD | 750 mg | 500 mg q48h |
| Uncomplicated UTI | No dosage adjustment required | |

Cl_{Cr}=creatinine clearances

CAPD=chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine Clearance (mL/min)

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

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 LEVAQUIN should not be taken, even if a dose is missed.

Administration

Tablets

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

Injection

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Levofloxacin injection should be infused intravenously, slowly over a period of not less than 60 minutes for a 250 mg or a 500 mg dose, and not less than 90 minutes for a 750 mg dose.

LEVAQUIN Injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration (see **WARNINGS AND PRECAUTIONS**).

LEVAQUIN Injection Premix in single-use flexible containers does not require further dilution. Consequently, each 50 mL, 100 mL and 150 mL of PREMIXED solution contains the equivalent of 250 mg, 500 mg and 750 mg of levofloxacin (5mg/mL), respectively in 5% Dextrose (D₅W).

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

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

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

Instructions for the Use of LEVAQUIN Injection PREMIX in flexible containers

To open

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

Preparation for administration

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

OVERDOSAGE

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

The administration of activated charcoal as soon as possible after oral overdose may prevent excessive increase of systemic levofloxacin exposure.

LEVAQUIN exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of LEVAQUIN: 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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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

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

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from other classes of antimicrobial agents, such as β -lactam antibiotics, aminoglycosides, and macrolides. Therefore, microorganisms resistant to these latter classes of antimicrobial agents may be susceptible to fluoroquinolones. For example, β -lactamase production and alterations in

penicillin-binding proteins have no effect on levofloxacin activity. Conversely, microorganisms resistant to fluoroquinolones may be susceptible to other classes of antimicrobial agents.

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 **DETAILED PHARMACOLOGY; Human Pharmacology; Studies Measuring the Effects on QT and Corrected QT (QTc) Intervals**).

Pharmacokinetics

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

Table 1.2 - Summary of Pharmacokinetic Parameters (mean ± SD)

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

^a healthy males 18-53 years of age;

^b 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose;

^c healthy male subjects 32-46 years of age;

^{cc} healthy male subjects 19-51 years of age;

^d including 500 mg q48h for 8 patients with moderate renal impairment (Cl_{Cr}20-50 mL/min) and infections of the respiratory tract or skin;

^e healthy males 22-75 years of age;

^f healthy females 18-80 years of age;

^g young healthy male and female subjects 18-36 years of age;

^h healthy elderly male and female subjects 66-80 years of age;

ⁱ dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modelling;

^j AUC for 0-∞ reported, unless otherwise specified;

^k male and female subjects 34-54 years of age;

^x AUC_{0-24 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

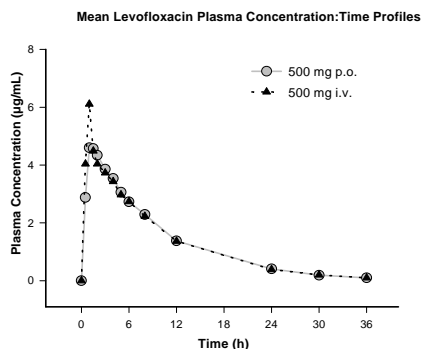
Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1 to 2 hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin is approximately 99% in both cases, demonstrating 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 1.2. Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in this patient population. Dosage adjustment may be required in such patients to avoid accumulation.

A dosage reduction is being recommended depending on the levels of renal insufficiency. Dosing recommendations are based on pharmacokinetic modeling of data collected from a clinical safety and pharmacokinetic study in renally impaired patients treated with a single 500 mg oral dose of levofloxacin (see **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

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

Injection

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

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Tablets

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

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

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

LEVAQUIN Tablets are packaged in bottles of 50 tablets.

LEVAQUIN levofloxacin Tablets contain the following inactive ingredients:

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

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

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

LEVAQUIN Injection

LEVAQUIN Injection in Premix flexible containers is a sterile, preservative-free, non-pyrogenic premixed solution that contains levofloxacin, at 5 mg/mL in 5% dextrose (D₅W). The solution has a pH ranging from 3.8 to 5.8. Solutions of hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH.

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

LEVAQUIN Injection is supplied in single-use flexible containers containing a premixed, ready-to-use levofloxacin solution in D₅W in the following formats:

- containers of 100 mL capacity containing 50 or 100 mL of PREMIXED solution
 - containers of 150 mL capacity containing 150 mL of PREMIXED solution
- Supplied in cases of 12 flexible containers

NO FURTHER DILUTION OF THESE PREPARATIONS ARE NECESSARY.

Consequently, each 50 mL, 100 mL and 150 mL of PREMIXED solution contains the equivalent of 250 mg, 500 mg and 750 mg of levofloxacin (5 mg/mL), respectively in 5% Dextrose (D₅W).

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

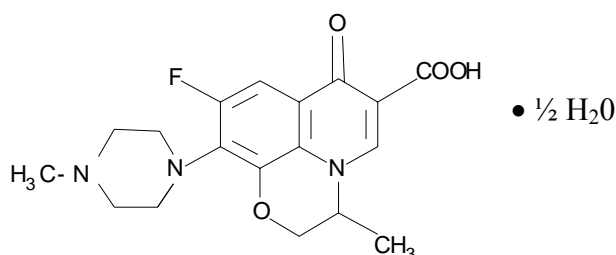
Proper name: levofloxacin

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: $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2} H_2O$

Molecular mass: 370.38

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 pK_a values for levofloxacin are 5.33 and 8.07 for pK_{a1} and pK_{a2} , respectively. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that, from pH 0.6 to 5.8, the solubility of levofloxacin is essentially constant (approximately 100 mg/mL). Levofloxacin is considered *soluble* to *freely soluble* in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL), and is considered *freely soluble* in this range.

Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9. Levofloxacin is considered *freely soluble* to *soluble* at the pH range of 6.7 to 7.7, beyond which the solubility begins to increase again.

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

CLINICAL TRIALS

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 (%) | |
|---------------------------------|---|--------|-------------------------------|---------|
| <i>Streptococcus pneumoniae</i> | 25/27 | (92.6) | 26/27 | (96.3) |
| <i>Haemophilus influenzae</i> | 19/21 | (90.5) | 25/27 | (92.6) |
| <i>Moraxella catarrhalis</i> | 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 (%) |
|--|---------------------------------|
| <i>Haemophilus influenzae</i> | 35/36 (97.2) |
| <i>Streptococcus pneumoniae</i> | 32/32 (100.0) |
| <i>Staphylococcus aureus</i> | 31/33 (93.9) |
| <i>Moraxella (Branhamella) catarrhalis</i> | 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 <i>S. pneumoniae</i> | 19/22 (86.4) |
| <i>Haemophilus influenzae</i> | 12/13 (92.3) |
| <i>Haemophilus parainfluenzae</i> | 12/12 (100.0) |
| <i>Mycoplasma pneumoniae</i> | 32/34 (94.1) |
| <i>Chlamydia pneumoniae</i> | 20/22 (90.9) |
| <i>Legionella pneumophila</i> | 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 pneumoniae* 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 (%) |
|--|---------------------------------|-------------------------------|
| <i>Chlamydia pneumoniae</i> | 46/47 (97.9) | 49/53 (92.5) |
| <i>Streptococcus pneumoniae</i> | 39/39 (100.0) | 39/40 (97.5) |
| <i>Haemophilus influenzae</i> | 30/30 (100.0) | 19/24 (79.2) |
| <i>Mycoplasma pneumoniae</i> | 19/19 (100.0) | 22/22 (100.0) |
| <i>Staphylococcus aureus</i> | 10/10 (100.0) | 9/9 (100.0) |
| <i>Haemophilus parainfluenzae</i> | 7/8 (87.5) | 15/21 (71.4) |
| <i>Moraxella (Branhamella) catarrhalis</i> | 7/7 (100.0) | 6/7 (85.7) |
| <i>Legionella pneumophila</i> | 5/5 (100.0) | 3/4 (75.0) |
| <i>Klebsiella pneumonia</i> | 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 (%) |
|--|---------------------------------|
| <i>Chlamydia pneumoniae</i> | 71/75 (94.7) |
| <i>Streptococcus pneumoniae</i> | 43/44 (97.7) |
| <i>Haemophilus influenzae</i> | 38/39 (97.4) |
| <i>Staphylococcus aureus</i> | 10/12 (83.3) |
| <i>Moraxella (Branhamella) catarrhalis</i> | 11/11 (100.0) |
| <i>Mycoplasma pneumoniae</i> | 10/10 (100.0) |
| <i>Haemophilus parainfluenzae</i> | 8/9 (88.9) |
| <i>Klebsiella pneumonia</i> | 7/7 (100.0) |
| <i>Legionella pneumophila</i> | 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=187 ^b | 58 (18-91) | 93/94 |
| | | oral amoxicillin 875 mg/clavulanate 125 mg twice daily for 10 days | n=182 ^b | 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 ^c | 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 (%) |
|-----------------------------------|-------------------------|-----------------------|
| <i>Staphylococcus aureus</i> | 4/5 (80.0) | 3/5 (60.0) |
| <i>Streptococcus pneumoniae</i> | 16/18 (88.9) | 10/13 (76.9) |
| <i>Haemophilus influenzae</i> | 25/30 (83.3) | 20/20 (100.0) |
| <i>Haemophilus parainfluenzae</i> | 18/20 (90.0) | 15/18 (83.3) |
| <i>Moraxella catarrhalis</i> | 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 (%) |
|--|-------------------------|-----------------------|
| <i>Haemophilus influenzae</i> | 21/21 (100.0) | 17/24 (70.8) |
| <i>Moraxella (Branhamella) catarrhalis</i> | 18/19 (94.7) | 8/8 (100.0) |
| <i>Haemophilus parainfluenzae</i> | 14/15 (93.3) | 7/7 (100.0) |
| <i>Pseudomonas aeruginosa</i> | 8/10 (80.0) | 11/14 (78.6) |
| <i>Streptococcus pneumoniae</i> | 9/10 (90.0) | 6/7 (85.7) |
| <i>Staphylococcus aureus</i> | 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 (%) |
|--|-------------------------|-----------------------|
| <i>Haemophilus influenzae</i> | 42/44 (95.5) | 29/31 (93.5) |
| <i>Haemophilus parainfluenzae</i> | 27/27 (100.0) | 30/32 (93.8) |
| <i>Moraxella (Branhamella) catarrhalis</i> | 25/25 (100.0) | 29/32 (90.6) |
| <i>Streptococcus pneumoniae</i> | 14/16 (87.5) | 10/10 (100.0) |
| <i>Staphylococcus aureus</i> | 10/10 (100.0) | 34/35 (97.1) |
| <i>Pseudomonas aeruginosa</i> | 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 (%) |
|---------------------------------|----------------------|--------------------|
| <i>Staphylococcus aureus</i> | 14/21 (66.7) | 13/19 (68.4) |
| <i>Pseudomonas aeruginosa</i> | 10/17 (58.8) | 5/17 (29.4) |
| <i>Haemophilus influenzae</i> | 13/16 (81.3) | 14/15 (93.3) |
| <i>Escherichia coli</i> | 10/12 (83.3) | 7/11 (63.6) |
| <i>Klebsiella pneumoniae</i> | 9/11 (81.8) | 6/7 (85.7) |
| <i>Serratia marcescenes</i> | 9/11 (81.8) | 2/7 (28.6) |
| <i>Streptococcus pneumoniae</i> | 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 (%) |
|-------------------------------|----------------------|--------------------|
| <i>Staphylococcus aureus</i> | 87/87 (100.0) | 76/87 (87.4) |
| <i>Streptococcus pyogenes</i> | 14/14 (100.0) | 18/20 (90.0) |
| <i>Pseudomonas aeruginosa</i> | 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 (%) |
|-------------------------------|----------------------|--------------------|
| <i>Staphylococcus aureus</i> | 66/70 (94.3) | 70/75 (93.3) |
| <i>Streptococcus pyogenes</i> | 17/18 (94.4) | 12/13 (92.3) |
| <i>Pseudomonas aeruginosa</i> | 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 days | 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 (%) |
|---------------------------------|----------------------|--------------------|
| <i>Staphylococcus aureus</i> | 50/56 (89.3) | 35/49 (71.4) |
| <i>Streptococcus faecalis</i> | 8/10 (80.0) | 6/11 (54.5) |
| <i>Streptococcus pyogenes</i> | 5/6 (83.3) | 6/7 (85.7) |
| <i>Proteus mirabilis</i> | 9/10 (90.0) | 7/12 (58.3) |
| <i>Streptococcus agalactiae</i> | 9/12 (75.0) | 9/13 (69.2) |
| <i>Pseudomonas aeruginosa</i> | 4/7 (57.1) | 5/6 (83.3) |

Complicated Urinary Tract Infection and Acute Pylonephritis

Study demographics and trial design

Table 2.32 - Summary of patient demographics for clinical trials in Complicated Urinary Tract Infection (cUTI) and Acute Pylonephritis (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 ($\geq 10^5$ 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 ($\geq 10^5$ 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

| <i>Pathogen</i> | <i>Levofloxacin 750 mg x 5 days</i> <i>n/N (%)</i> | | | <i>Comparator</i> <i>n/N (%)</i> | | |
|---|---|-----------------|------------------|-------------------------------------|-----------------|------------------|
| mITT Population | | | | | | |
| | Overall | AP | cUTI | Overall | AP | cUTI |
| <i>Escherichia coli</i> | 165/206 (80.1) | 67/81 (82.7) | 98/125 (78.4) | 158/216 (73.1) | 70/89 (78.7) | 88/127 (69.3) |
| <i>Klebsiella pneumoniae</i> | 21/29 (72.4) | | 19/26 (73.1) | 26/29 (89.7) | | 22/25 (88.0) |
| <i>Proteus mirabilis</i> | 13/13 (100.0) | | 10/10 (100.0) | 6/7 (85.7) | | 6/7 (85.7) |
| <i>Escherichia coli</i> with bacteremia | | 7/12 (58.3) | | | 8/12 (66.7) | |
| Microbiologically Evaluable Population | | | | | | |
| | Overall | AP | cUTI | Overall | AP | cUTI |
| <i>Escherichia coli</i> | 155/172 (90.1) | 63/69 (91.3) | 92/103 (89.3) | 148/168 (88.1) | 63/67 (94.0) | 85/101 (84.2) |
| <i>Klebsiella pneumoniae</i> | 20/23 (87.0) | | 18/21 (85.7) | 24/26 (92.3) | | 21/23 (91.3) |
| <i>Proteus mirabilis</i> | 12/12 (100.0) | | 9/9 (100.0) | 6/6 (100.0) | | 6/6 (100.0) |
| <i>Escherichia coli</i> 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 (%) |
|-------------------------------|---------------------------------|-------------------------------|
| <i>Escherichia coli</i> | 88/92 (95.7) | 96/99 (97.0) |
| <i>Klebsiella pneumonia</i> | 31/32 (96.9) | 22/23 (95.7) |
| <i>Streptococcus faecalis</i> | 8/9 (88.9) | 6/11 (54.5) |
| <i>Proteus mirabilis</i> | 13/14 (92.9) | 5/5 (100.0) |
| <i>Pseudomonas aeruginosa</i> | 7/12 (58.3) | 7/7 (100.0) |
| <i>Enterobacter cloacae</i> | 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 (%) |
|-------------------------------|---------------------------------|-------------------------------|
| <i>Escherichia coli</i> | 118/119 (99.2) | 116/118 (98.3) |
| <i>Klebsiella pneumonia</i> | 29/31 (93.5) | 23/25 (92.0) |
| <i>Proteus mirabilis</i> | 11/11 (100.0) | 9/9 (100.0) |
| <i>Streptococcus faecalis</i> | 4/8 (50.0) | 6/8 (75.0) |
| <i>Pseudomonas aeruginosa</i> | 8/9 (88.9) | 4/6 (66.7) |
| <i>Enterobacter cloacae</i> | 6/7 (85.7) | 4/6 (66.7) |

Uncomplicated Urinary Tract Infections

Study demographics and trial design

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 (%) |
|-------------------------------------|----------------------|--------------------|
| <i>Escherichia coli</i> | 125/127 (98.4) | 131/138 (94.9) |
| <i>Klebsiella pneumoniae</i> | 10/11 (90.9) | 8/8 (100.0) |
| <i>Staphylococcus saprophyticus</i> | 8/8 (100.0) | 3/3 (100.0) |
| <i>Staphylococcus aureus</i> | 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 (%) |
|---------------------------------|-------------------------|-----------------------|
| <i>Escherichia coli</i> | 14/15 (93.3) | 9/11 (81.8) |
| <i>Enterococcus faecalis</i> | 39/54 (72.2) | 34/45 (75.6) |
| <i>Staphylococcus epidermis</i> | 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 |
| Cardiopulmonary System | dog | ≥6 mg/kg, i.v. bolus, decreases in blood pressure, left ventricular pressure, respiration depth; ≤10 mg/kg, i.v. infusion, no effect on blood pressure; ≥20 mg/kg, i.v. infusion, decrease in blood pressure, decrease in cardiac output and stroke volume; increase in serum histamine concentrations |
| Gastrointestinal System | mouse | At 200 mg/kg, i.v., inhibition of gastric propulsion |
| | rat | ≥200 mg/kg, p.o., decrease in gastric fluid volume, total acidity, pepsin output; increase in gastric fluid pH; at 600 mg/kg, decrease in gastric emptying; at 200 mg/kg, i.v., decrease in gastric fluid volume, acid and pepsin output and gastric emptying; increase in gastric pH |
| Urinary Tract | rat | ≥200 mg/kg, p.o., decrease in urinary volume and electrolyte excretion; at 200 mg/kg, i.v., decrease in urinary volume |
| Inflammation | rat | At 600 mg/kg, p.o., inhibition of carrageenan-induced foot edema |
| Isolated Smooth Muscle | | On dog mesenteric, renal, femoral, and basilar arteries, inhibition of norepinephrine-induced contractions $\geq 10 \times 10^{-6}$ 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 C_{max} (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 C_{max} 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)

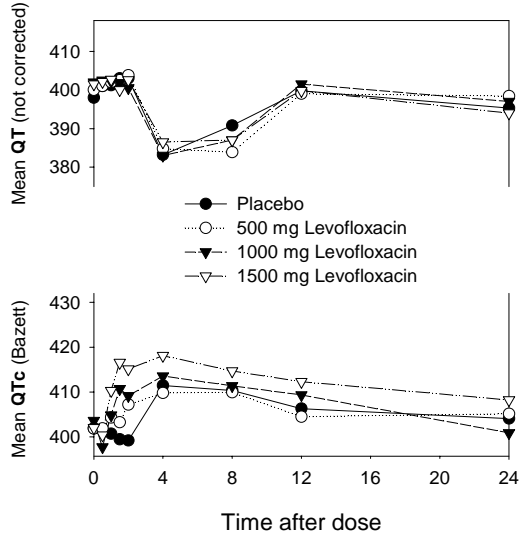
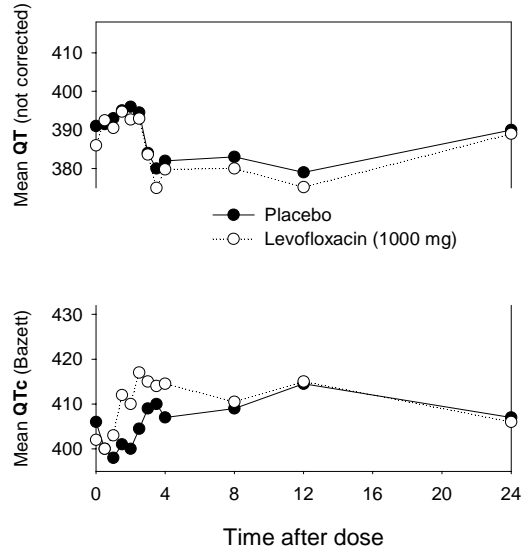


FIGURE B
 Mean QT and QTc Bazett versus
 Time after Dose of Placebo
 or 1000 mg of Levofloxacin
 (Comparative Study n=48)



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 \pm SD):

| Oral Dose (mg) | n | Peak Plasma Concentration ($\mu\text{g/mL}$) | Area Under the Curve ($\text{AUC}_{0-\infty}$, $\mu\text{g}\cdot\text{h/mL}$) |
|-------------------|----|---|---|
| 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 $\mu\text{g/mL}$ after the 500 mg doses, and 8.6 and 1.1 $\mu\text{g/mL}$ 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 q12h | 89% | 94% | 71% |

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

Urine Concentrations

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

| Collection Interval | Cl _{Cr} 50-80 mL/min n ^b = 3 | Cl _{Cr} 20-49 mL/min n = 8 | Cl _{Cr} <20 mL/min n = 6 |
|---------------------|---|--|--------------------------------------|
| 0__6 h | 185±61.7 | 98.1±48.1 | 66.5±27.3 |
| 6__12 h | 91.6±24.4 | 75.2±22.1 | 39.0±23.1 |
| 12__24 h | 156±183 | 58.6±31.1 | 29.5±20.7 |
| 24__36 h | 49.7±16.2 | 44.1±10.6 | <25 |
| 36__48 h | <25 | <25 | <25 |

^a Limit of quantitation = 25 µg/mL

^b n = number of subjects

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

| Collection Interval | Cl _{Cr} 50-80 mL/min receiving 250 mg q24 h | Cl _{Cr} 20-49 mL/min receiving 250 mg q24h | Cl _{Cr} <20 mL/min receiving 250 mg q48h |
|---------------------|--|---|---|
| 0__6 h | 161 | 103 | 54 |
| 6__12 h | 61 | 76 | 29 |
| 12__24 h | 40 | 58 | 24 |
| 24__36 h | – | – | 23 |
| 36__48 h | – | – | 16 |

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

Hepatic Insufficiency

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

Bacterial Infection

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

HIV Infection

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

Drug-Drug Interactions

The potential for pharmacokinetic drug interactions between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, zidovudine and antacids has been evaluated (see **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 the following table.

Table 2.48 - In Vitro Activity of Levofloxacin against Clinical Isolates

| Organism | # of isolates) | MIC ($\mu\text{g/mL}$) | | |
|--|----------------|--------------------------|---------|------------------------|
| | | 50% | 90% | Range |
| <i>Acinetobacter baumannii</i> | (57) | 0.120 | 16.000 | 0.060- >16.000 |
| <i>Acinetobacter calcoaceticus</i> | (48) | 0.250 | 0.250 | 0.030- 64.000 |
| <i>Chlamydia pneumoniae</i> | (10) | 0.250 | 0.250 | 0.125- 0.500 |
| <i>Citrobacter diversus</i> | (20) | 0.030 | 0.030 | 0.015- 0.060 |
| <i>Citrobacter freundii</i> | (50) | 0.060 | 1.000 | 0.015- 8.000 |
| <i>Enterobacter spp.</i> | (200) | 0.060 | 0.500 | ≤ 0.008 - >16.000 |
| <i>Enterobacter aerogenes</i> | (44) | 0.250 | 0.500 | 0.060- 2.000 |
| <i>Enterobacter agglomerans</i> | (13) | 0.250 | 0.250 | 0.060- 0.500 |
| <i>Enterobacter cloacae</i> | (97) | 0.250 | 0.500 | 0.025- 16.000 |
| <i>Enterococcus spp.</i> | (162) | 1.000 | >16.000 | 0.500- >16.000 |
| <i>Enterococcus (Streptococcus) faecalis</i> | (122) | 1.000 | 16.000 | 0.250- 64.000 |
| <i>Escherichia coli</i> | (817) | 0.030 | 0.060 | ≤ 0.008 - >16.000 |
| <i>Haemophilus influenzae</i> | (94) | 0.015 | 0.015 | ≤ 0.008 - 0.030 |
| <i>Haemophilus parainfluenzae</i> | (127) | 0.250 | 0.250 | 0.015- 1.000 |
| <i>Haemophilus parahemolyticus</i> | (12) | 0.250 | 0.250 | 0.008- 0.250 |
| <i>Klebsiella spp.</i> | (345) | 0.060 | 1.000 | 0.015- 16.000 |
| <i>Klebsiella oxytoca</i> | (43) | 0.250 | 0.250 | 0.030- 2.000 |
| <i>Klebsiella pneumoniae</i> | (225) | 0.250 | 0.500 | 0.060- 18.000 |
| <i>Legionella pneumophila</i> | (10) | | 0.030 | 0.0079- 0.030 |
| <i>Moraxella (Branhamella) catarrhalis</i> | (110) | 0.250 | 0.250 | 0.0150- 1.000 |
| <i>Morganella morganii</i> | (43) | 0.060 | 1.000 | 0.0150- >16.000 |
| <i>Mycoplasma pneumoniae</i> | (60) | 0.250 | 0.500 | 0.250- 0.500 |
| <i>Neisseria gonorrhoeae</i> | (47) | ≤ 0.008 | 0.016 | ≤ 0.008 - 0.060 |
| <i>Neisseria meningitides</i> | (13) | 0.250 | 0.250 | 0.250- 0.500 |
| <i>Proteus and Providencia spp.</i> | (36) | 0.060 | 1.000 | 0.015- >16.000 |
| <i>Proteus mirabilis</i> | (123) | 0.060 | 0.120 | 0.015- 4.000 |
| <i>Proteus vulgaris</i> | (14) | 0.250 | 0.250 | 0.250- 0.500 |
| <i>Pseudomonas aeruginosa*</i> | (378) | 1.000 | 8.000 | 0.030- >16.000 |
| <i>Pseudomonas maltophilia</i> | (17) | 0.500 | 2.000 | 0.250- 4.000 |
| <i>Salmonella spp.</i> | (10) | 0.060 | 0.060 | 0.060- 0.250 |
| <i>Serratia spp.</i> | (65) | 0.120 | 0.500 | 0.030- >16.000 |
| <i>Serratia marcescens</i> | (42) | 0.250 | 1.000 | 0.125- 4.000 |
| <i>Staphylococcus aureus</i> | (565) | 0.250 | 0.500 | 0.125- 32.000 |
| <i>Staphylococcus aureus</i> , methicillin-resistant (MRSA)** | (25) | 0.250 | 0.500 | 0.120- 1.000 |
| <i>Staphylococcus aureus</i> , methicillin-susceptible (MSSA) | (25) | 0.250 | 0.500 | 0.120- 0.500 |
| <i>Staphylococcus aureus</i> , oxacillin-resistant | (62) | 8.000 | >16.000 | 0.120- >16.000 |
| <i>Staphylococcus aureus</i> , oxacillin-susceptible | (367) | 0.120 | 0.500 | 0.030- 16.000 |

| Organism | (# of isolates) | MIC ($\mu\text{g/mL}$) | | |
|--|-----------------|--------------------------|--------|-------------------------|
| | | 50% | 90% | Range |
| <i>Staphylococcus epidermidis</i> | (47) | 0.250 | 8.000 | 0.250- 32.000 |
| <i>Staphylococcus epidermidis</i> , methicillin-resistant (MRSE) | (14) | 0.250 | 0.250 | 0.120- 0.500 |
| <i>Staphylococcus epidermidis</i> , methicillin-susceptible (MSSE) | (12) | 0.250 | 1.000 | 0.250- 1.000 |
| <i>Staphylococcus saprophyticus</i> | (16) | 0.500 | 1.000 | 0.250- 2.000 |
| <i>Stenotrophomonas maltophilia</i> | (43) | 2.000 | 16.000 | 0.250- 16.000 |
| <i>Streptococcus (Viridans group)</i> | (8) | 0.750 | 1.000 | 0.250- 1.000 |
| <i>Streptococcus (Group C)</i> | (28) | 0.500 | 1.000 | 0.250- 2.000 |
| <i>Streptococcus (Group G)</i> | (34) | 0.500 | 1.000 | 0.250- 2.000 |
| <i>Streptococcus agalactiae</i> | (96) | 1.000 | 2.000 | 0.500- 2.000 |
| <i>Streptococcus milleri</i> | (35) | 0.500 | 1.000 | 0.250- 4.000 |
| <i>Streptococcus pneumoniae</i> | (99) | 1.000 | 1.000 | 0.500- 2.000 |
| <i>Streptococcus pneumoniae</i> , penicillin-susceptible (MIC $\leq 0.06\mu\text{g/mL}$) [‡] | (2699) | 0.500 | 1.000 | ≤ 0.004 - >8.000 |
| <i>Streptococcus pneumoniae</i> , penicillin-resistant (MIC $\geq 2.0\mu\text{g/mL}$) [‡] | (538) | 0.500 | 1.000 | ≤ 0.004 - 2.000 |
| <i>Streptococcus pneumoniae</i> , clarithromycin-susceptible (MIC $\leq 0.25\mu\text{g/mL}$) [‡] | (502) | 0.500 | 1.000 | 0.250- >16.000 |
| <i>Streptococcus pneumoniae</i> , clarithromycin-resistant (MIC $\geq 1.0\mu\text{g/mL}$) [‡] | (136) | 1.000 | 2.000 | 0.12- 16.000 |
| <i>Streptococcus pneumoniae</i> , erythromycin-resistant (MIC $\geq 1.0\mu\text{g/mL}$) [‡] | (27) | 1.000 | 1.000 | 0.500- 16.000 |
| <i>Streptococcus pyogenes</i> | (87) | 0.500 | 1.000 | 0.250- 2.000 |
| <i>Streptococcus sanguis</i> | (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*:

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤2 | Susceptible (S) |
| 4 | Intermediate (I) |
| ≥8 | Resistant (R) |

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*:^a

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤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

| <u>MIC (µg/mL)</u> | <u>Interpretation</u> |
|--------------------|-----------------------|
| ≤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:

| <u>Microorganism</u> | | <u>MIC (µg/mL)</u> |
|---------------------------------|-------------------------|--------------------|
| <i>Enterococcus faecalis</i> | ATCC 29212 | 0.25 - 2 |
| <i>Escherichia coli</i> | ATCC 25922 | 0.008 - 0.06 |
| <i>Escherichia coli</i> | ATCC 35218 | 0.015 - 0.06 |
| <i>Pseudomonas aeruginosa</i> | ATCC 27853 | 0.5 - 4 |
| <i>Staphylococcus aureus</i> | ATCC 29213 | 0.06 - 0.5 |
| <i>Haemophilus influenzae</i> | ATCC 49247 ^c | 0.008 - 0.03 |
| <i>Streptococcus pneumoniae</i> | 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*:

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥ 17 | Susceptible (S) |
| 14-16 | Intermediate (I) |
| ≤ 13 | Resistant (R) |

For *Haemophilus influenzae* and *Haemophilus parainfluenzae*:^e

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥ 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

| <u>Zone diameter (mm)</u> | <u>Interpretation</u> |
|---------------------------|-----------------------|
| ≥ 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% CO₂.

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:

| <u>Microorganism</u> | | <u>Zone Diameter (mm)</u> |
|---------------------------------|-------------------------|---------------------------|
| <i>Escherichia coli</i> | ATCC 25922 | 29 - 37 |
| <i>Pseudomonas aeruginosa</i> | ATCC 27853 | 19 - 26 |
| <i>Staphylococcus aureus</i> | ATCC 25923 | 25 - 30 |
| <i>Haemophilus influenzae</i> | ATCC 49247 ^g | 32 - 40 |
| <i>Streptococcus pneumoniae</i> | 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.

* REFERENCES

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

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 |
| 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 ♀), ↓ β-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 | i.v. | Lethality: None. Clin Obs: Histamine-like effects at 15 and 60 mg/kg, |

| Species, Age/Grp/No., Sex/Grp | Route, Dosage, Duration | Results |
|--|----------------------------------|---|
| 4-5 mo old 5 grp 3 ♂/grp | 0, 2, 4, 15, 60 2 wk | ↓ bw gain and fc at 60 mg/kg. Clin Path: ↑ plasma fibrinogen and urine specific gravity; ↓ serum Fe. Micro: ↓ absolute liver weight at 60 mg/kg and ↓ absolute and relative testes weight at 4, 15, and 60 mg/kg; and thrombus formation in injected vessels at 60 mg/kg, arthropathy and delayed testicular maturation at ≥4 mg/kg. NOAEL = 2 mg/kg/day. TI = 0.28 |
| Dog 18 mo old 3 grp 3 ♂/grp | i.v. 0, 10, 30 2 wk | Lethality: None. Clin Obs: Histamine-like effects and ↓ activity at 10 and 30 mg/kg. Signs subsided by 30 min post-administration except ↓ activity. Clin Path: NSF. Micro: NSF. NOAEL for arthropathy = 30 mg/kg/day. TI = 4.2 |
| Dog 7-8 mo old 4 grp 3 ♀ & 3 ♂/grp | infusion 0, 3, 10, 30 4 wk | Lethality: None. Clin Obs: Histamine-like effects in a dosage-related manner. Clin Path: NSF. Micro: Arthropathy at ≥10 mg/kg/day. NOAEL = 3 mg/kg/day. TI = 0.42 |
| 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/day 24/sex/group | salivation (at 60 mg/kg mostly ♂ and at 360 mg/kg ♀ & ♂) and soft stool at 360 mg/kg; ↑ wc at 360 mg/kg for ♂ and ≥ 60 mg/kg for ♀; ↓ in placental weights at 360 mg/kg. No effect on mating performance. | No effect on intrauterine survival or fetal development. | None |
| Intravenous, rat 0, 10, 30, 100 mg/kg/day 24/sex/group | swollen tail, soft feces, and urinary incontinence at 100 mg/kg in ♂ and ♀. In females, ↓ bw gain and fc (wk 1 only) at 100 mg/kg. In males, ↓ bw gain ≥30 and slight ↓ fc at all levels, enlarged cecum ≥30 mg/kg. No effect on reproductive performance. NOAEL = 10 mg/kg/day for ♂ rats, 30 mg/kg/day for ♀ rats. | No effect on intrauterine survival or development. Slight non-dose-related ↑ in resorptions. NOAEL = 100 mg/kg/day for in utero exposure for rat fetuses. | None |

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

^a In both studies, males (8 weeks old) were administered levofloxacin daily for 9 weeks prior to mating, throughout the mating period, and until necropsy. The females (11-12 weeks old) were treated daily for 2 weeks prior to mating, throughout the mating period, and for 7 days after copulation.

NOAEL = No Observable Adverse Effect Level.

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 LEVAQUIN*
levofloxacin

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

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 LEVAQUIN is not helping you get better, or if you feel worse.

ABOUT THIS MEDICATION

What the medication is used for:

LEVAQUIN is from a group of antibiotics known as quinolones. LEVAQUIN is used to treat adults with certain lung, sinus, skin and urinary tract infections caused by certain germs called bacteria.

What it does:

LEVAQUIN has been shown, in a large number of clinical trials, to be effective for the treatment of bacterial infections. LEVAQUIN 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). LEVAQUIN, like other antibiotics, does not kill viruses.

When it should not be used:

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

What the medicinal ingredient is:

LEVAQUIN contains the active (medicinal) ingredient levofloxacin.

What the nonmedicinal ingredients are:

Tablets

All LEVAQUIN tablets contain hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide and polysorbate 80. In addition, the 250 mg tablets also contain synthetic red iron oxide, and the 500 mg tablets also contain synthetic red and yellow iron oxides.

Injection

dextrose, water for injection
Solutions of hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH.

What dosage forms it comes in:

LEVAQUIN tablets are available in 250 mg, 500 mg or 750 mg strengths. LEVAQUIN tablets are terra cotta pink for the 250 mg tablet, peach coloured for the 500 mg tablet, or white for the 750 mg tablet.

LEVAQUIN injection is available in a single-use flexible container, containing a premixed, ready-to-use levofloxacin solution:

- Containers of 100 mL capacity containing 50 or 100 mL of premixed solution.
- Containers of 150 mL capacity containing 150 mL premixed solution.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- LEVAQUIN 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 LEVAQUIN.
- 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.
- LEVAQUIN should not be used by pregnant women unless the doctor determines the possible benefit outweighs the possible risk to the fetus.
- LEVAQUIN is not recommended for use by nursing mothers as the effects on the infant are unknown. Your doctor will decide whether you should discontinue nursing your baby or discontinue LEVAQUIN.
- LEVAQUIN is not recommended for children under the age of 18 years.

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

BEFORE you use LEVAQUIN 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 LEVAQUIN may interfere with blood sugar levels.

INTERACTIONS WITH THIS MEDICATION

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

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

Taking warfarin and LEVAQUIN 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 LEVAQUIN and may prevent it from working properly. You should take LEVAQUIN either two hours before or two hours after taking these products.

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

PROPER USE OF THIS MEDICATION

Usual Adult dose:

LEVAQUIN 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.

LEVAQUIN injection is to be administered intravenously.

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:

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

Missed dose:

Do not take more than the prescribed dose of LEVAQUIN even if you missed a dose by mistake. You should not take a double dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

LEVAQUIN is generally well tolerated. The most common side effects caused by LEVAQUIN, 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 LEVAQUIN tablets, even after just one dose. If you develop hives, itching, skin rash, difficulty breathing or swallowing, swelling in the face, tongue or throat, or other symptoms of an allergic reaction, you should stop taking this medication and call your doctor.

LEVAQUIN may be associated with dizziness. You should know how you react to this drug before you operate an automobile, or machinery, or 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 LEVAQUIN. The risk of tendon effects is higher if you are over 65 years old, and especially of you are taking corticosteroids. If you develop pain, swelling, or rupture of a tendon you should stop taking LEVAQUIN, avoid exercise and strenuous use of the affected area and contact your doctor.

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

Quinolones, including LEVAQUIN, 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 LEVAQUIN 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 LEVAQUIN 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). LEVAQUIN has been infrequently associated with phototoxicity. You should avoid excessive exposure to sunlight or artificial ultraviolet light while you are taking LEVAQUIN. 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 LEVAQUIN tablets, you should stop taking LEVAQUIN 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 have been reported in patients taking LEVAQUIN. 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 heart beat on an electrocardiogram test, and with abnormal heart rhythm. Very rare cases of abnormal heart beat have been reported in patients while on LEVAQUIN, but these reports generally involved patients who had conditions that predisposed them to abnormal heart beat, or who have been taking other medicines that increase the risk of developing abnormal heart beat. If you develop heart palpitations (fast beating) or have fainting spells, you should stop taking LEVAQUIN 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 LEVAQUIN tablets. If you develop a watery and bloody stool with or without stomach cramps and fever, contact your doctor as soon as possible.

These are not all the side effects that have been reported with LEVAQUIN. If you notice any side effects not mentioned in this leaflet, or you have concerns about the side effects you are experiencing, please inform your doctor.

| | | |
|---|---|---|
| reaction | | |
| <ul style="list-style-type: none"> • skin rash • hives • itching • difficulty breathing or swallowing • swelling of face, tongue or throat | | |
| Symptoms of neuropathy | | ✓ |
| <ul style="list-style-type: none"> • pain • burning • tingling • numbness • weakness | | |
| If you have diabetes and you develop a hypoglycemic reaction. | | ✓ |
| Symptoms of hypoglycemia | ✓ | |
| <ul style="list-style-type: none"> • dizziness • excessive hunger • lack of coordination • headache • fatigue • fainting | | |
| Symptoms of hyperglycemia | ✓ | |
| <ul style="list-style-type: none"> • excessive thirst • excessive urination | | |
| Symptoms of liver problems | ✓ | |
| <ul style="list-style-type: none"> • 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 LEVAQUIN, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15°– 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.

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 call your doctor or pharmacist |
|--|-----------------------------------|---|
| Rare | | |
| Heart palpitations (fast beating) or fainting spells | | ✓ |
| Tendon pain, swelling or rupture | | ✓ |
| Symptoms of allergic | | ✓ |

REPORTING SUSPECTED SIDE EFFECTS

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance:

By toll-free telephone: 866-234-2345
By toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

By regular mail:
Canada Vigilance National Office
Marketed Health Products Safety and Effectiveness
Information Bureau
Marketed Health Products Directorate
Health Products and Food Branch
Health Canada
Tunney's Pasture, AL 0701C
Ottawa, ON K1A 0K9

***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 found at:

<http://www.janssen-ortho.com>

or by contacting the sponsor, Janssen-Ortho Inc., at:

1-800-567-3331

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