HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LEVAQUIN® safely and effectively. See full prescribing information for LEVAQUIN®.

LEVAQUIN® (levofloxacin) Tablet, Film Coated for Oral use
LEVAQUIN® (levofloxacin) Solution for Oral use
LEVAQUIN® (levofloxacin) Injection, Solution, Concentrate for Intravenous use
LEVAQUIN® (levofloxacin) Injection, Solution for Intravenous use
Initial U.S. Approval: 1996

WARNING:
See full prescribing information for complete boxed warning.
Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants *[See Warnings and Precautions (5.1)]*. Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[See Warnings and Precautions (5.2)]*.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® and other antibacterial drugs, LEVAQUIN® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.

RECENT MAJOR CHANGES

Warnings and Precautions
- Peripheral Neuropathy (5.8) 07/2013

INDICATIONS AND USAGE

LEVAQUIN® is a fluoroquinolone antibacterial indicated in adults (≥18 years of age) with infections caused by designated, susceptible bacteria (1, 12.4).
- Pneumonia: nosocomial (1.1) and community acquired (1.2, 1.3)
- Acute bacterial sinusitis (1.4)
- Acute bacterial exacerbation of chronic bronchitis (1.5)
- Skin and skin structure infections: complicated (1.6) and uncomplicated (1.7)
- Chronic bacterial prostatitis (1.8)
- Urinary tract infections: complicated (1.9, 1.10) and uncomplicated (1.12)
- Acute pyelonephritis (1.11)
- Inhalational anthrax, post-exposure (1.13)
- Plague (1.14)

DOSAGE AND ADMINISTRATION

- Dosage in patients with normal renal function (2.1)

Type of Infection	Dose Every 24 hours	Duration (days)
Nosocomial Pneumonia (1.1)	750 mg	7–14
Community Acquired Pneumonia (1.2)	500 mg	7–14
Community Acquired Pneumonia (1.3)	750 mg	5
Acute Bacterial Sinusitis (1.4)	750 mg	5
	500 mg	10–14
Acute Bacterial Exacerbation of Chronic Bronchitis (1.5)	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI) (1.6)	750 mg	7–14
Uncomplicated SSSI (1.7)	500 mg	7–10
Chronic Bacterial Prostatitis (1.8)	500 mg	28
Complicated Urinary Tract Infection (1.9) or Acute Pyelonephritis (1.11)	750 mg	5
Complicated Urinary Tract Infection (1.10) or Acute Pyelonephritis (1.11)	250 mg	10
Uncomplicated Urinary Tract Infection (1.12)	250 mg	3

Type of Infection	Dose Every 24 hours	Duration (days)
Inhalational Anthrax (Post-Exposure) (1.13)		
Adults and Pediatric Patients > 50 kg	500 mg	60
Pediatric Patients < 50 kg and ≥ 6 months of age	8 mg/kg BID (not to exceed 250 mg/dose)	60
Plague (1.14)		
Adults and Pediatric Patients > 50 kg	500 mg	10 to 14
Pediatric Patients < 50 kg and ≥ 6 months of age	8 mg/kg BID (not to exceed 250 mg/dose)	10 to 14

- Adjust dose for creatinine clearance < 50 mL/min (2.3, 8.6, 12.3)
- IV Injection, Single-Use or Premix: Slow IV infusion only, over 60 or 90 minutes depending on dose. Avoid rapid or bolus IV (2.5)
- Dilute single-use vials to 5 mg/mL prior to IV infusion (2.6)
- Do not mix with other medications in vial or IV line (2.6)

DOSAGE FORMS AND STRENGTHS

Formulation (3)	Strength
Tablets	250 mg, 500 mg, and 750 mg
Oral Solution	25 mg/mL
Injection: single-use vials for dilution	500 mg in 20 mL 750 mg in 30 mL
Injection: premix single-use flexible containers	250 mg in 50 mL 500 mg in 100 mL 750 mg in 150 mL

CONTRAINDICATIONS

Known hypersensitivity to LEVAQUIN® or other quinolones (4, 5.3)

WARNINGS AND PRECAUTIONS

- Risk of tendinitis and tendon rupture is increased. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs (5.1, 8.5)
- May exacerbate muscle weakness in persons with myasthenia gravis. Avoid use in patients with a known history of myasthenia gravis (5.2)
- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4, 5.3)
- Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.4)
- Hepatotoxicity: Severe, and sometimes fatal, hepatoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur (5.5)
- Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. Increased intracranial pressure (pseudotumor cerebri) has been reported (5.6)
- *Clostridium difficile*-associated colitis: evaluate if diarrhea occurs (5.7)
- Peripheral neuropathy: discontinue immediately if symptoms occur in order to prevent irreversibility (5.8)
- Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval (5.9, 8.5)

ADVERSE REACTIONS

The most common reactions (≥3%) were nausea, headache, diarrhea, insomnia, constipation and dizziness (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Pharmaceuticals, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

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Interacting Drug	Interaction
Multivalent cation-containing products including antacids, metal cations or didanosine	Absorption of levofloxacin is decreased when the tablet or oral solution formulation is taken within 2 hours of these products. Do not co-administer the intravenous formulation in the same IV line with a multivalent cation, e.g., magnesium (2.4, 7.1)
Warfarin	Effect may be enhanced. Monitor prothrombin time, INR, watch for bleeding (7.2)
Antidiabetic agents	Carefully monitor blood glucose (5.11, 7.3)

USE IN SPECIFIC POPULATIONS

- **Geriatrics:** Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older (5.5, 8.5, 17). May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use (5.1, 8.5, 17). May be more susceptible to prolongation of the QT interval. (5.9, 8.5, 17).
- **Pediatrics:** Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more LEVAQUIN®-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.10, 8.4, 13.2). Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) (1.13, 2.2, 8.4, 14.9) and plague (1.14, .2.2, 8.4, 14.10)

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide

Revised: 05/2014

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FULL PRESCRIBING INFORMATION

WARNING:

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants *[See Warnings and Precautions (5.1)]*.

Fluoroquinolones, including LEVAQUIN®, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[See Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

To reduce the development of drug-resistant bacteria and maintain the effectiveness of LEVAQUIN® and other antibacterial drugs, LEVAQUIN® should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

LEVAQUIN® Tablets/Injection and Oral Solution are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed in this section. LEVAQUIN® Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form).

Culture and susceptibility testing

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin *[see Microbiology (12.4)]*. Therapy with LEVAQUIN® may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

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As with other drugs in this class, some isolates of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with LEVAQUIN®. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

1.1 Nosocomial Pneumonia

LEVAQUIN® is indicated for the treatment of 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 *[see Clinical Studies (14.1)]*.

1.2 Community-Acquired Pneumonia: 7–14 day Treatment Regimen

LEVAQUIN® is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae* (including multi-drug-resistant *Streptococcus pneumoniae* [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae [see Dosage and Administration (2.1)* and *Clinical Studies (14.2)]*.

MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

1.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of community-acquired pneumonia due to *Streptococcus pneumoniae* (excluding multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae [see Dosage and Administration (2.1)* and *Clinical Studies (14.3)]*.

1.4 Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

LEVAQUIN® is indicated for the treatment of acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis [see Clinical Studies (14.4)]*.

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1.5 Acute Bacterial Exacerbation of Chronic Bronchitis

LEVAQUIN® is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*.

1.6 Complicated Skin and Skin Structure Infections

LEVAQUIN® is indicated for the treatment of complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis [see Clinical Studies (14.5)]*.

1.7 Uncomplicated Skin and Skin Structure Infections

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

1.8 Chronic Bacterial Prostatitis

LEVAQUIN® is indicated for the treatment of chronic bacterial prostatitis due to *Escherichia coli*, *Enterococcus faecalis*, or methicillin-susceptible *Staphylococcus epidermidis [see Clinical Studies (14.6)]*.

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis [see Clinical Studies (14.7)]*.

1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa [see Clinical Studies (14.8)]*.

1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen

LEVAQUIN® is indicated for the treatment of acute pyelonephritis caused by *Escherichia coli*, including cases with concurrent bacteremia *[see Clinical Studies (14.7, 14.8)]*.

1.12 Uncomplicated Urinary Tract Infections

LEVAQUIN® is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli*, *Klebsiella pneumoniae*, or *Staphylococcus saprophyticus*.

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1.13 Inhalational Anthrax (Post-Exposure)

LEVAQUIN® is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. The effectiveness of LEVAQUIN® is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. LEVAQUIN® has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of LEVAQUIN® in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk *[see Dosage and Administration (2.1, 2.2)* and *Clinical Studies (14.9)]*.

1.14 Plague

LEVAQUIN® is indicated for treatment of plague, including pneumonic and septicemic plague, due to *Yersinia pestis* (*Y. pestis*) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older. Efficacy studies of LEVAQUIN® could not be conducted in humans with plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals *[see Dosage and Administration (2.1, 2.2)* and *Clinical Studies (14.10)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Patients with Normal Renal Function

The usual dose of LEVAQUIN® Tablets or Oral Solution is 250 mg, 500 mg, or 750 mg administered orally every 24 hours, as indicated by infection and described in Table 1. The usual dose of LEVAQUIN® Injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in Table 1.

These recommendations apply to patients with creatinine clearance ≥ 50 mL/min. For patients with creatinine clearance <50 mL/min, adjustments to the dosing regimen are required *[see Dosage and Administration (2.3)]*.

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

Type of Infection*	Dosed Every 24 hours	Duration (days)†
Nosocomial Pneumonia	750 mg	7–14
Community Acquired Pneumonia‡	500 mg	7–14
Community Acquired Pneumonia§	750 mg	5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10–14

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

Type of Infection[*]	Dosed Every 24 hours	Duration (days)[†]
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7–14
Uncomplicated SSSI	500 mg	7–10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[¶]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[#]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg [Þ,ß] Pediatric patients < 50 kg and ≥ 6 months of age [Þ,ß]	500 mg see Table 2 below (2.2)	60[ß] 60[ß]
Plague, adult and pediatric patients > 50 kg [à] Pediatric patients < 50 kg and ≥ 6 months of age	500 mg see Table 2 below (2.2)	10 to 14 10 to 14

[*] Due to the designated pathogens *[see Indications and Usage (1)]*.

[†] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

[‡] Due to methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae* (including multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila*, or *Mycoplasma pneumoniae [see Indications and Usage (1.2)]*.

[§] Due to *Streptococcus pneumoniae* (excluding multi-drug-resistant isolates [MDRSP]), *Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Indications and Usage (1.3)]*.

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

[#] This regimen is indicated for cUTI due to *Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa*; and for AP due to *E. coli*.

[Þ] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*.

[ß] The safety of LEVAQUIN® in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients *[see Warnings and Precautions (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)]*. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk.

[à] Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*. Higher doses of LEVAQUIN® typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

2.2 Dosage in Pediatric Patients

The dosage in pediatric patients ≥ 6 months of age is described below in Table 2.

Table 2: Dosage in Pediatric Patients ≥ 6 months of age

Type of Infection[*]	Dose	Freq. Once every	Duration[†]
Inhalational Anthrax (post-exposure)[‡,§]			
Pediatric patients > 50 kg	500 mg	24 hr	60 days[§]
Pediatric patients < 50 kg and ≥ 6 months of age	8 mg/kg (not to exceed 250 mg per dose)	12 hr	60 days[§]

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Table 2: Dosage in Pediatric Patients ≥ 6 months of age

Plague[¶]			
Pediatric patients > 50 kg	500 mg	24 hr	10 to 14 days
Pediatric patients < 50 kg and ≥ 6 months of age	8 mg/kg (not to exceed 250 mg per dose)	12 hr	10 to 14 days

[*] Due to *Bacillus anthracis [see Indications and Usage (1.13)]* and *Yersinia pestis* [*see Indications and Usage (1.14)*].

[†] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.

[‡] Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized *B. anthracis*. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit *[see Clinical Studies (14.9)]*

[§] The safety of LEVAQUIN® in pediatric patients for durations of therapy beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients *[see Warnings and Precautions (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)]*. Prolonged LEVAQUIN® therapy should only be used when the benefit outweighs the risk.

[¶] Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*.

2.3 Dosage Adjustment in Adults with Renal Impairment

Administer LEVAQUIN® with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced.

No adjustment is necessary for patients with a creatinine clearance ≥ 50 mL/min.

In patients with impaired renal function (creatinine clearance <50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance *[see Use in Specific Populations (8.6)]*.

Table 3 shows how to adjust dose based on creatinine clearance.

Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (creatinine clearance <50 mL/min)

Dosage in Normal Renal Function Every 24 hours	**Creatinine Clearance 20 to 49 mL/min**	**Creatinine Clearance 10 to 19 mL/min**	**Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)**
750 mg	750 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours
500 mg	500 mg initial dose, then 250 mg every 24 hours	500 mg initial dose, then 250 mg every 48 hours	500 mg initial dose, then 250 mg every 48 hours
250 mg	No dosage adjustment required	250 mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment is required	No information on dosing adjustment is available

2.4 Drug Interaction With Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

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LEVAQUIN® Tablets and Oral Solution

LEVAQUIN® Tablets and Oral Solution should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable/buffered tablets or the pediatric powder for oral solution *[see Drug Interactions (7.1)* and *Patient Counseling Information (17.2)]*.

LEVAQUIN® Injection

LEVAQUIN® Injection should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line *[see Dosage and Administration (2.6)]*.

2.5 Administration Instructions

Food and LEVAQUIN® Tablets and Oral Solution

LEVAQUIN® Tablets can be administered without regard to food. It is recommended that LEVAQUIN® Oral Solution be taken 1 hour before or 2 hours after eating.

LEVAQUIN® Injection

Caution: Rapid or bolus intravenous infusion of LEVAQUIN® has been associated with hypotension and must be avoided. LEVAQUIN® Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. LEVAQUIN® Injection should be administered only by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Hydration for Patients Receiving LEVAQUIN® Tablets, Oral Solution, and Injection

Adequate hydration of patients receiving oral or intravenous LEVAQUIN® should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones *[see Adverse Reactions (6.1)* and *Patient Counseling Information (17.2)]*.

2.6 Preparation of Intravenous Product

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Because only limited data are available on the compatibility of LEVAQUIN® Injection with other intravenous substances, additives or other medications should not be added to

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LEVAQUIN® Injection Premix in Single-Use Flexible Containers and LEVAQUIN® Injection in Single-Use Vials, or infused simultaneously through the same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of LEVAQUIN® Injection with an infusion solution compatible with LEVAQUIN® Injection and with any other drug(s) administered via this common line.

LEVAQUIN® Injection in Single-Use Vials

Single-use vials require dilution prior to administration.

LEVAQUIN® Injection is supplied in single-use vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) and 750 mg (30 mL vial) of levofloxacin in Water for Injection, USP. The 20 mL and 30 mL vials each contain 25 mg of levofloxacin/mL. These LEVAQUIN® Injection single-use vials must be further diluted with an appropriate solution prior to intravenous administration *[see Table 4]*. The concentration of the resulting diluted solution should be 5 mg/mL prior to administration.

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

Table 4: Compatible Intravenous Solutions

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

Since no preservative or bacteriostatic agent is present in this product, aseptic technique must be used in preparation of the final intravenous solution. Since the vials are for single-use only, any unused portion remaining in the vial should be discarded. When used to prepare two 250 mg doses from the 20 mL vial containing 500 mg of levofloxacin, the full content of the vial should be withdrawn at once using a single-entry procedure, and a second dose should be prepared and stored for subsequent use *[see Stability of LEVAQUIN® Injection Following Dilution]*.

Prepare the desired dosage of levofloxacin according to Table 5:

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Table 5: Preparation of LEVAQUIN® Intravenous Solution

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

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

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

Stability of LEVAQUIN® Injection Following Dilution: LEVAQUIN® Injection, when diluted in a compatible intravenous fluid to a concentration of 5 mg/mL, is stable for 72 hours when stored at or below 25°C (77°F) and for 14 days when stored under refrigeration at 5°C (41°F) in plastic intravenous containers. Solutions that are diluted in a compatible intravenous solution and frozen in glass bottles or plastic intravenous containers are stable for 6 months when stored at - 20°C (- 4°F). Thaw frozen solutions at room temperature 25°C (77°F) or in a refrigerator 8°C (46°F). Do not force thaw by microwave irradiation or water bath immersion. Do not refreeze after initial thawing.

LEVAQUIN® Injection Premix in Single-Use Flexible Containers (5 mg/mL)

LEVAQUIN® Injection is also supplied in flexible containers within a foil overwrap. These contain a premixed, ready to use levofloxacin solution in 5% dextrose (D5W) for single-use. The 100 mL premixed flexible containers contain either 250 mg/50 mL or 500 mg/100 mL of levofloxacin solution. The 150 mL flexible container contains 750 mg/150 mL of levofloxacin solution. The concentration of each container is 5 mg/mL. No further dilution of these preparations is necessary. Because the premix flexible containers are for single-use only, any unused portion should be discarded.

Instructions for the Use of LEVAQUIN® Injection Premix in Flexible Containers:

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.

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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 Premix in Flexible Containers.
6. Open flow control clamp to expel air from set. Close clamp.
7. Regulate rate of administration with flow control clamp.

3 DOSAGE FORMS AND STRENGTHS

TABLETS, Film-coated, capsule-shaped

- 250 mg terra cotta pink tablets, imprinted with "250" on one side and "LEVAQUIN" on the other
- 500 mg peach tablets, imprinted with "500" on one side and "LEVAQUIN" on the other
- 750 mg white tablets, imprinted with "750" on one side and "LEVAQUIN" on the other

ORAL SOLUTION, 25 mg/mL, clear yellow to clear greenish-yellow color

INJECTION, Single-Use Vials of concentrated solution for dilution for intravenous infusion, clear yellow to clear greenish-yellow in appearance

- 20 mL vial of 25 mg/mL levofloxacin solution, equivalent to 500 mg of levofloxacin
- 30 mL vial of 25 mg/mL levofloxacin solution, equivalent to 750 mg of levofloxacin

INJECTION (5 mg/mL in 5% Dextrose) Premix in Single-Use Flexible Containers, for intravenous infusion

- 100 mL container, fill volume 50 mL (equivalent to 250 mg levofloxacin)
- 100 mL container, fill volume 100 mL (equivalent to 500 mg levofloxacin)
- 150 mL container, fill volume 150 mL (equivalent to 750 mg levofloxacin)

4 CONTRAINDICATIONS

LEVAQUIN® is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials *[see Warnings and Precautions (5.3)]*.

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5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

Fluoroquinolones, including LEVAQUIN®, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. LEVAQUIN® should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug. *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.3)]*.

5.2 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including LEVAQUIN®, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid LEVAQUIN® in patients with a known history of myasthenia gravis *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.3)]*.

5.3 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including LEVAQUIN®. 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. LEVAQUIN® should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious

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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 (6); Patient Counseling Information (17.3)]*.

5.4 Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolones, including LEVAQUIN®. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestations may include one or more of the following:

- fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);
- vasculitis; arthralgia; myalgia; serum sickness;
- allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- hepatitis; jaundice; acute hepatic necrosis or failure;
- anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive measures instituted *[see Adverse Reactions (6); Patient Counseling Information (17.3)]*.

5.5 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with LEVAQUIN®. 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 *[see Warnings and Precautions (5.4)]*. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Adverse Reactions (6); Patient Counseling Information (17.3)]*.

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5.6 Central Nervous System Effects

Convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones, including LEVAQUIN®. Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving LEVAQUIN®, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, LEVAQUIN® should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). *[see Adverse Reactions (6)*; *Drug Interactions (7.4, 7.5)*; *Patient Counseling Information (17.3)]*.

5.7 *Clostridium difficile*-Associated Diarrhea

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

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated *[see Adverse Reactions (6.2), Patient Counseling Information (17.3)]*.

5.8 Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including LEVAQUIN®. Symptoms may occur soon after initiation of LEVAQUIN® and may be irreversible. LEVAQUIN® should be discontinued

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immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation *[see Adverse Reactions (6), Patient Counseling Information (17.3)]*.

5.9 Prolongation of the QT Interval

Some fluoroquinolones, including LEVAQUIN®, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including LEVAQUIN®. LEVAQUIN® should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval *[see Adverse Reactions (6.3), Use in Specific Populations (8.5)*, and *Patient Counseling Information (17.3)]*.

5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

LEVAQUIN® is indicated in pediatric patients (6 months of age and older) only for the prevention of inhalational anthrax (post-exposure) and for plague *[see Indications and Usage (1.13, 1.14)*]. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving LEVAQUIN® *[see Use in Specific Populations (8.4)]*.

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluoroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species *[see Animal Toxicology and/or Pharmacology (13.2)]*.

5.11 Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with LEVAQUIN®, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with LEVAQUIN®, LEVAQUIN®

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should be discontinued and appropriate therapy should be initiated immediately *[see Adverse Reactions (6.2)*; *Drug Interactions (7.3)*; *Patient Counseling Information (17.4)]*.

5.12 Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.3)]*.

5.13 Development of Drug Resistant Bacteria

Prescribing LEVAQUIN® in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria *[see Patient Counseling Information (17.1)]*.

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions

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

- Tendon Effects *[see Warnings and Precautions (5.1)]*
- Exacerbation of Myasthenia Gravis *[see Warnings and Precautions (5.2)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.3)]*
- Other Serious and Sometimes Fatal Reactions *[see Warnings and Precautions (5.4)]*
- Hepatotoxicity *[see Warnings and Precautions (5.5)]*
- Central Nervous System Effects *[see Warnings and Precautions (5.6)]*
- *Clostridium difficile*-Associated Diarrhea *[see Warnings and Precautions (5.7)]*
- Peripheral Neuropathy that may be irreversible *[see Warnings and Precautions (5.8)]*
- Prolongation of the QT Interval *[see Warnings and Precautions (5.9)]*
- Musculoskeletal Disorders in Pediatric Patients *[see Warnings and Precautions (5.10)]*
- Blood Glucose Disturbances *[see Warnings and Precautions (5.11)]*
- Photosensitivity/Phototoxicity *[see Warnings and Precautions (5.12)]*
- Development of Drug Resistant Bacteria *[see Warnings and Precautions (5.13)]*

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Hypotension has been associated with rapid or bolus intravenous infusion of LEVAQUIN®. LEVAQUIN® should be infused slowly over 60 to 90 minutes, depending on dosage *[see Dosage and Administration (2.5)]*.

Crystalluria and cylindruria have been reported with quinolones, including LEVAQUIN®. Therefore, adequate hydration of patients receiving LEVAQUIN® should be maintained to prevent the formation of a highly concentrated urine *[see Dosage and Administration (2.5)]*.

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to LEVAQUIN® in 7537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with LEVAQUIN® for a wide variety of infectious diseases *[see Indications and Usage (1)]*. Patients received LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3–14 days, and the mean number of days on therapy was 10 days.

The overall incidence, type and distribution of adverse reactions was similar in patients receiving LEVAQUIN® doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of LEVAQUIN® due to adverse drug reactions occurred in 4.3% of patients overall, 3.8% of patients treated with the 250 mg and 500 mg doses and 5.4% of patients treated with the 750 mg dose. The most common adverse drug reactions leading to discontinuation with the 250 and 500 mg doses were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and headache (0.2%). The most common adverse drug reactions leading to discontinuation with the 750 mg dose were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

Adverse reactions occurring in ≥1% of LEVAQUIN®-treated patients and less common adverse reactions, occurring in 0.1 to <1% of LEVAQUIN®-treated patients, are shown in Table 6 and Table 7, respectively. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

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Table 6: Common (≥1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN®

System/Organ Class	Adverse Reaction	% (N=7537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia* *[see Warnings and Precautions (5.6)]*	4
Nervous System Disorders	headache dizziness *[see Warnings and Precautions (5.6)]*	6 3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea *[see Warnings and Precautions (5.3)]*	1
Gastrointestinal Disorders	nausea diarrhea constipation abdominal pain vomiting dyspepsia	7 5 3 2 2 2
Skin and Subcutaneous Tissue Disorders	rash *[see Warnings and Precautions (5.3)]* pruritus	2 1
Reproductive System and Breast Disorders	vaginitis	1†
General Disorders and Administration Site Conditions	edema injection site reaction chest pain	1 1 1

* N=7274
† N=3758 (women)

Table 7: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN® (N=7537)

System/Organ Class	Adverse Reaction
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia thrombocytopenia granulocytopenia *[see Warnings and Precautions (5.4)]*
Immune System Disorders	allergic reaction *[see Warnings and Precautions (5.3,5.4)]*
Metabolism and Nutrition Disorders	hyperglycemia hypoglycemia *[see Warnings and Precautions (5.11)]* hyperkalemia
Psychiatric Disorders	anxiety agitation confusion depression hallucination nightmare* *[see Warnings and Precautions (5.6)]*

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Table 7: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with LEVAQUIN® (N=7537)

System/Organ Class	Adverse Reaction
	sleep disorder* anorexia abnormal dreaming*
Nervous System Disorders	tremor convulsions *[see Warnings and Precautions (5.6)]* paresthesia *[see Warnings and Precautions (5.8)]* vertigo hypertonia hyperkinesias abnormal gait somnolence* syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest palpitation ventricular tachycardia ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis stomatitis pancreatitis esophagitis gastroenteritis glossitis pseudomembranous/ *C. difficile* colitis *[see Warnings and Precautions (5.7)]*
Hepatobiliary Disorders	abnormal hepatic function increased hepatic enzymes increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	urticaria *[see Warnings and Precautions (5.3)]*
Musculoskeletal and Connective Tissue Disorders	arthralgia tendinitis *[see Warnings and Precautions (5.1)]* myalgia skeletal pain
Renal and Urinary Disorders	abnormal renal function acute renal failure *[see Warnings and Precautions (5.4)]*

* N = 7274

In clinical trials using multiple-dose therapy, ophthalmologic abnormalities, including cataracts and multiple punctate lenticular opacities, have been noted in patients undergoing treatment

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with quinolones, including LEVAQUIN®. The relationship of the drugs to these events is not presently established.

6.3 Postmarketing Experience

Table 8 lists adverse reactions that have been identified during post-approval use of LEVAQUIN®. 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 8: Postmarketing Reports Of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders	pancytopenia aplastic anemia leukopenia hemolytic anemia *[see Warnings and Precautions (5.4)]* eosinophilia
Immune System Disorders	hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions anaphylactic shock angioneurotic edema serum sickness *[see Warnings and Precautions (5.3, 5.4)]*
Psychiatric Disorders	psychosis paranoia isolated reports of suicide attempt and suicidal ideation *[see Warnings and Precautions (5.6)]*
Nervous System Disorders	exacerbation of myasthenia gravis *[see Warnings and Precautions (5.2)]* anosmia ageusia parosmia dysgeusia peripheral neuropathy (may be irreversible) *[see Warnings and Precautions (5.8)]* isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudotumor cerebri *[see Warnings and Precautions (5.6)]*
Eye Disorders	Uveitis vision disturbance, including diplopia visual acuity reduced vision blurred scotoma
Ear and Labyrinth Disorders	hypoacusis tinnitus

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Table 8: Postmarketing Reports Of Adverse Drug Reactions

System/Organ Class	Adverse Reaction
Cardiac Disorders	isolated reports of torsade de pointes electrocardiogram QT prolonged *[see Warnings and Precautions (5.9)]* tachycardia
Vascular Disorders	vasodilatation
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis *[see Warnings and Precautions (5.4)]*
Hepatobiliary Disorders	hepatic failure (including fatal cases) hepatitis jaundice *[see Warnings and Precautions (5.4), (5.5)]*
Skin and Subcutaneous Tissue Disorders	bullous eruptions to include: Stevens-Johnson Syndrome toxic epidermal necrolysis erythema multiforme *[see Warnings and Precautions (5.4)]* photosensitivity/phototoxicity reaction *[see Warnings and Precautions (5.12)]* leukocytoclastic vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture *[see Warnings and Precautions (5.1)]* muscle injury, including rupture rhabdomyolysis
Renal and Urinary Disorders	interstitial nephritis *[see Warnings and Precautions (5.4)]*
General Disorders and Administration Site Conditions	multi-organ failure pyrexia
Investigations	prothrombin time prolonged international normalized ratio prolonged muscle enzymes increased

7 DRUG INTERACTIONS

7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

LEVAQUIN® Tablets and Oral Solution

While the chelation by divalent cations is less marked than with other fluoroquinolones, concurrent administration of LEVAQUIN® Tablets and Oral Solution with antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. Tablets with antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after oral LEVAQUIN® administration.

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LEVAQUIN® Injection

There are no data concerning an interaction of intravenous fluoroquinolones with oral antacids, sucralfate, multivitamins, didanosine, or metal cations. However, no fluoroquinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line *[see Dosage and Administration (2.5)]*.

7.2 Warfarin

No significant effect of LEVAQUIN® on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, there have been reports during the postmarketing experience in patients that LEVAQUIN® enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and LEVAQUIN® use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if LEVAQUIN® is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding *[see Adverse Reactions (6.3)*; *Patient Counseling Information (17.4)]*.

7.3 Antidiabetic Agents

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with fluoroquinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered *[see Warnings and Precautions (5.11)*; *Adverse Reactions (6.2), Patient Counseling Information (17.4)]*.

7.4 Non-Steroidal Anti-Inflammatory Drugs

The concomitant administration of a non-steroidal anti-inflammatory drug with a fluoroquinolone, including LEVAQUIN®, may increase the risk of CNS stimulation and convulsive seizures *[see Warnings and Precautions (5.6)]*.

7.5 Theophylline

No significant effect of LEVAQUIN® on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient

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population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when LEVAQUIN® is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels *[see Warnings and Precautions (5.6)]*.

7.6 Cyclosporine

No significant effect of LEVAQUIN® on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other fluoroquinolones. Levofloxacin C_{max} and k_e were slightly lower while T_{max} and $t_{½}$ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for LEVAQUIN® or cyclosporine when administered concomitantly.

7.7 Digoxin

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

7.8 Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the C_{max} of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and $t_{½}$ of levofloxacin were higher while CL/F and CL_R were lower during concomitant treatment of LEVAQUIN® with probenecid or cimetidine compared to LEVAQUIN® alone. However, these changes do not warrant dosage adjustment for LEVAQUIN® when probenecid or cimetidine is co-administered.

7.9 Interactions with Laboratory or Diagnostic Testing

Some fluoroquinolones, including LEVAQUIN®, 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based

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upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

There are, however, no adequate and well-controlled studies in pregnant women. LEVAQUIN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers

Based on data on other fluoroquinolones and very limited data on LEVAQUIN®, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from LEVAQUIN® 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.

8.4 Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. *[see Warnings and Precautions (5.10)* and *Animal Toxicology and/or Pharmacology (13.2)]*.

<u>Pharmacokinetics following intravenous administration</u>

The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients resulting in lower plasma exposures than adults for a given mg/kg dose *[see Clinical Pharmacology (12.3)* and *Clinical Studies (14.9)]*.

<u>Inhalational Anthrax (Post-Exposure)</u>

Levofloxacin is indicated in pediatric patients 6 months of age and older, for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied *[see Indications and Usage (1.13), Dosage and Administration (2.2)* and *Clinical Studies (14.9)]*.

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Plague

Levofloxacin is indicated in pediatric patients, 6 months of age and older, for treatment of plague, including pneumonic and septicemic plague due to *Yersinia pestis* (*Y. pestis*) and prophylaxis for plague. Efficacy studies of LEVAQUIN® could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate *[see Indications and Usage (1.14), Dosage and Administration (2.2)* and *Clinical Studies (14.10)]*.

Safety and effectiveness in pediatric patients below the age of six months have not been established.

Adverse Events

In clinical trials, 1534 children (6 months to 16 years of age) were treated with oral and intravenous LEVAQUIN®. Children 6 months to 5 years of age received LEVAQUIN® 10 mg/kg twice a day and children greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days.

A subset of children in the clinical trials (1340 LEVAQUIN®-treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) during 60 days and 1 year following the first dose of the study drug. Children treated with LEVAQUIN® had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 9.

Table 9: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

Follow-up Period	**LEVAQUIN® N = 1340**	**Non-Fluoroquinolone* N = 893**	**p-value†**
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year‡	46 (3.4%)	16 (1.8%)	p = 0.025

* Non-Fluoroquinolone: ceftriaxone, amoxicillin/clavulanate, clarithromycin

† 2-sided Fisher's Exact Test

‡ There were 1199 LEVAQUIN®-treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders was calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%)

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LEVAQUIN®-treated children and most were treated with analgesics. The median time to resolution was 7 days for LEVAQUIN®-treated children and 9 for non-fluoroquinolone-treated children (approximately 80% resolved within 2 months in both groups). No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.

Vomiting and diarrhea were the most frequently reported adverse events, occurring in similar frequency in the LEVAQUIN®-treated and non-fluoroquinolone-treated children.

In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience *[see Adverse Reactions (6)]* may also be expected to occur in pediatric patients.

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as LEVAQUIN®. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing LEVAQUIN® to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue LEVAQUIN® and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur *[see Boxed Warning*; *Warnings and Precautions (5.1)*; and *Adverse Reactions (6.3)]*.

In phase 3 clinical trials, 1,945 LEVAQUIN®-treated patients (26%) were ≥ 65 years of age. Of these, 1,081 patients (14%) were between the ages of 65 and 74 and 864 patients (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with LEVAQUIN®. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. LEVAQUIN® should be discontinued immediately if the patient develops signs and symptoms of hepatitis *[see Warnings and Precautions (5.5)]*.

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using LEVAQUIN® with concomitant drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in

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patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) *[see Warnings and Precautions (5.9)]*.

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However, since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of LEVAQUIN® are not required following hemodialysis or CAPD *[see Dosage and Administration (2.3)]*.

8.7 Hepatic Impairment

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.

10 OVERDOSAGE

In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

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.

11 DESCRIPTION

LEVAQUIN® is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-

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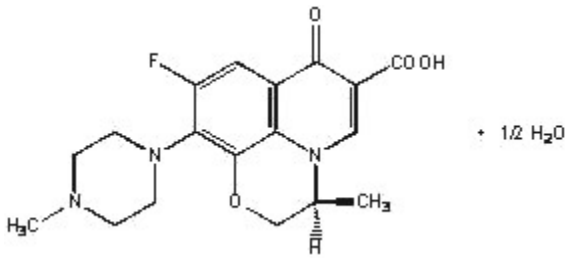
2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

Figure 1 : **The Chemical Structure of Levofloxacin**



The empirical formula is $C_{18}H_{20}FN_3O_4$ • ½ H_2O and the molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. 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 has the potential to form stable coordination compounds with many metal ions. This *in vitro* chelation potential has the following formation order: $Al^{+3}>Cu^{+2}>Zn^{+2}>Mg^{+2}>Ca^{+2}$.

Excipients and Description of Dosage Forms

<u>LEVAQUIN® Tablets</u>

LEVAQUIN® Tablets are available as film-coated tablets and contain the following inactive ingredients:

- 250 mg (as expressed in the anhydrous form): crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, synthetic red iron oxide and titanium dioxide.
- 500 mg (as expressed in the anhydrous form): crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, synthetic red and yellow iron oxides and titanium dioxide.

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- 750 mg (as expressed in the anhydrous form): crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, titanium dioxide.

LEVAQUIN® Oral Solution

LEVAQUIN® Oral Solution, 25 mg/mL, is a multi-use self-preserving aqueous solution of levofloxacin with pH ranging from 5.0 to 6.0. The appearance of LEVAQUIN® Oral Solution may range from clear yellow to clear greenish-yellow. This does not adversely affect product potency.

LEVAQUIN® Oral Solution contains the following inactive ingredients: artificial and natural flavors, ascorbic acid, benzyl alcohol, caramel color, glycerin, hydrochloric acid, propylene glycol, purified water, sucralose and sucrose. It may also contain a solution of sodium hydroxide for pH adjustment.

LEVAQUIN® Injection

The appearance of LEVAQUIN® Injection may range from a clear yellow to a clear greenish-yellow solution. This does not adversely affect product potency.

LEVAQUIN® Injection in Single-Use Vials is a sterile, preservative-free aqueous solution of levofloxacin in Water for Injection, with pH ranging from 3.8 to 5.8.

LEVAQUIN® Injection Premix in Single-Use Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging from 3.8 to 5.8. This is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D_5W). Solutions of hydrochloric acid and 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Levofloxacin is a member of the fluoroquinolone class of antibacterial agents *[see Microbiology (12.4)]*.

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12.3 Pharmacokinetics

The mean ± SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral tablet, oral solution, or intravenous (IV) doses of LEVAQUIN® are summarized in Table 10.

Table 10: Mean ± SD Levofloxacin PK Parameters

Regimen	C_{max} (mcg/mL)	T_{max} (h)	AUC (mcg·h/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	$t_{1/2}$ (h)	CL_R (mL/min)
Single dose							
250 mg oral tablet[3]	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21
500 mg oral tablet[3]*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg oral solution[12]	5.8 ± 1.8	0.8 ± 0.7	47.8 ± 10.8	183 ± 40	112 ± 37.2	7.0 ± 1.4	ND
500 mg IV[3]	6.2 ± 1.0	1.0 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg oral tablet[5]*	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg IV[5]	11.5 ± 4.0[4]	ND	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg every 24h oral tablet[3]	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg every 24h IV[3]	6.4 ± 0.8	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7.0 ± 0.8	99 ± 28
500 mg or 250 mg every 24h IV, patients with bacterial infection[6]	8.7± 4.0[7]	ND	72.5 ± 51.2[7]	154 ± 72	111 ± 58	ND	ND
750 mg every 24h oral tablet[5]	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg every 24h IV[5]	12.1 ± 4.1[4]	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg oral tablet single dose, effects of gender and age:							
Male[8]	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female[9]	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
Young[10]	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6.0 ± 0.9	140 ± 33
Elderly[11]	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2.0	91 ± 29
500 mg oral single dose tablet, patients with renal insufficiency:							
CLCR 50–80 mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	88 ± 10	ND	9.1 ± 0.9	57 ± 8
CLCR 20–49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CLCR <20 mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	ND

[1] clearance/bioavailability

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Table 10: Mean ± SD Levofloxacin PK Parameters

[2] volume of distribution/bioavailability
[3] healthy males 18–53 years of age
[4] 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose
[5] healthy male and female subjects 18–54 years of age
[6] 500 mg every 48h for patients with moderate renal impairment (CLCR 20–50 mL/min) and infections of the respiratory tract or skin
[7] dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling
[8] healthy males 22–75 years of age
[9] healthy females 18–80 years of age
[10] young healthy male and female subjects 18–36 years of age
[11] healthy elderly male and female subjects 66–80 years of age
[12] healthy males and females 19–55 years of age.

* Absolute bioavailability; F=0.99 ± 0.08 from a 500 mg tablet and F=0.99 ± 0.06 from a 750 mg tablet;
ND=not determined.

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of levofloxacin from a 500 mg tablet and a 750 mg tablet of LEVAQUIN® are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of LEVAQUIN® to healthy volunteers, the mean ± SD peak plasma concentration attained was 6.2 ± 1.0 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5 ± 4.0 mcg/mL after a 750 mg dose infused over 90 minutes. LEVAQUIN® Oral Solution and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ± 1.4 and 0.5 ± 0.2 mcg/mL after the 500 mg doses, and 8.6 ± 1.9 and 1.1 ± 0.4 mcg/mL after the 750 mg doses, respectively. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately 6.4 ± 0.8 and 0.6 ± 0.2 mcg/mL after the 500 mg doses, and 12.1 ± 4.1 and 1.3 ± 0.71 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500 mg dose of LEVAQUIN® with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, LEVAQUIN® Tablets can be administered without regard to food. It is recommended that LEVAQUIN® Oral Solution be taken 1 hour before or 2 hours after eating.

The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for LEVAQUIN® Tablets when equal

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doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable *(see Figure 2 and Figure 3)*.

Figure 2: Mean Levofloxacin Plasma Concentration vs. Time Profile: 750 mg

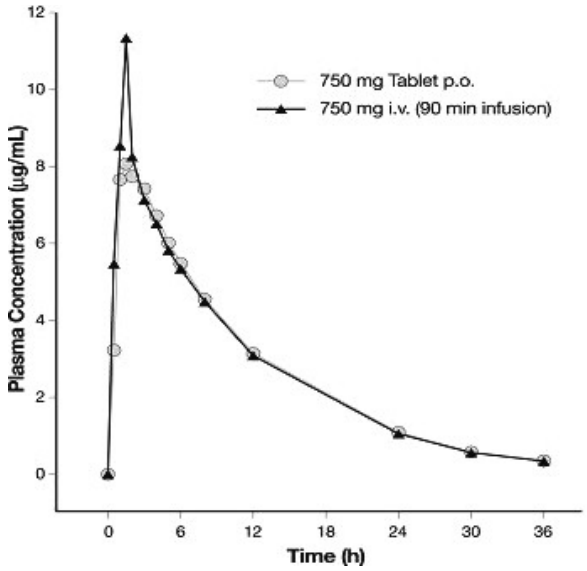
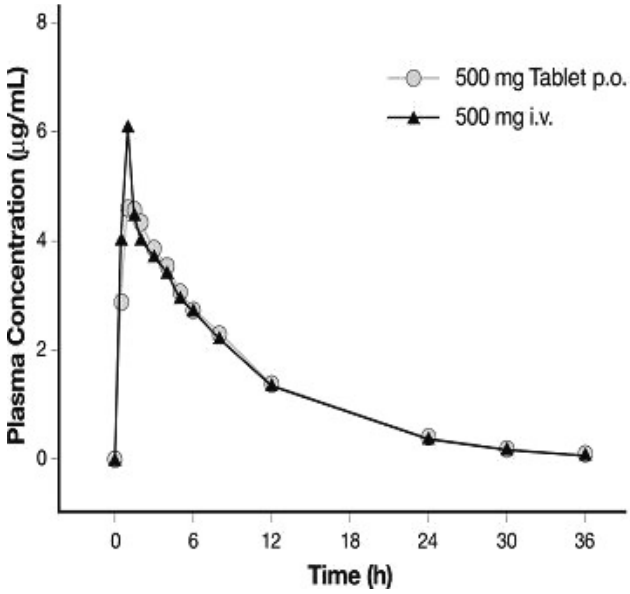


Figure 3: Mean Levofloxacin Plasma Concentration vs. Time Profile: 500 mg



Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is

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approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg doses of LEVAQUIN®, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5-fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

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

Metabolism

Levofloxacin 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

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally 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, respectively, 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 LEVAQUIN®.

Geriatric

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into

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consideration. Following a 500 mg oral dose of LEVAQUIN® 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. LEVAQUIN® dose adjustment based on age alone is not necessary *[see Use in Specific Populations (8.5)]*.

Pediatrics

The pharmacokinetics of levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC_{0-24} and C_{max}) to those observed in adult patients administered 500 mg of levofloxacin once every 24 hours.

Gender

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of LEVAQUIN® 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 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in adult patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of

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levofloxacin from the body, indicating that supplemental doses of LEVAQUIN® are not required following hemodialysis or CAPD *[see Dosage and Administration (2.3), Use in Specific Populations (8.6)]*.

Hepatic Impairment

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 *[see Use in Specific Populations (8.7)]*.

Bacterial Infection

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

Drug-Drug Interactions

The potential for pharmacokinetic drug interactions between LEVAQUIN® and antacids, warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated *[see Drug Interactions (7)]*.

12.4 Microbiology

Mechanism of Action

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Mechanism of Resistance

Fluoroquinolone resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV, termed the Quinolone-Resistance Determining Regions (QRDRs), or through altered efflux.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation *in vitro* is a rare occurrence (range: 10^{-9} to 10^{-10}). Cross-resistance has been observed between levofloxacin and some other

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fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Activity *in vitro* and *in vivo*

Levofloxacin has *in vitro* activity against Gram-negative and Gram-positive bacteria.

Levofloxacin has been shown to be active against most isolates of the following bacteria both *in vitro* and in clinical infections as described in *Indications and Usage (1)*:

Gram-Positive Bacteria

Enterococcus faecalis

Staphylococcus aureus (methicillin-susceptible isolates)

Staphylococcus epidermidis (methicillin-susceptible isolates)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP][1])

Streptococcus pyogenes

Gram-Negative Bacteria

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

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

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Pseudomonas aeruginosa

Serratia marcescens

Other Bacteria

Chlamydophila pneumoniae

Mycoplasma pneumoniae

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

Gram-Positive Bacteria

Staphylococcus haemolyticus

β-hemolytic *Streptococcus (Group C/F)*

β-hemolytic *Streptococcus (Group G)*

Streptococcus agalactiae

Streptococcus milleri

Viridans group *streptococci*

Bacillus anthracis

Gram-Negative Bacteria

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter koseri

Citrobacter freundii

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Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Yersinia pestis

Anaerobic Gram-Positive Bacteria

Clostridium perfringens

Susceptibility Tests

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in the resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.

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 MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method[1,2,4] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 11.

Diffusion techniques:

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Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg levofloxacin to test the susceptibility of bacteria to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according to the criteria outlined in Table 11.

Table 11: Susceptibility Test Interpretive Criteria for Levofloxacin

	Minimum Inhibitory Concentrations (mcg/mL)			**Disk Diffusion (zone diameter in mm)**		
Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
Enterobacteriaceae	≤2	4	≥8	≥17	14–16	≤13
Enterococcus faecalis	≤2	4	≥8	≥17	14–16	≤13
Staphylococcus species	≤2	4	≥8	≥17	14–16	≤13
Pseudomonas aeruginosa	≤2	4	≥8	≥17	14–16	≤13
Haemophilus influenzae	≤2	--[†]	--	≥17	--	--
Haemophilus parainfluenzae	≤2	--	--	≥17	--	--
Streptococcus pneumoniae	≤2	4	≥8	≥17	14–16	≤13
Streptococcus pyogenes	≤2	4	≥8	≥17	14–16	≤13
Yersinia pestis[4]	≤0.25	--	--	--	--	--
Bacillus anthracis[4]	≤0.25	--	--	--	--	--

S = Susceptible, I = Intermediate, R = Resistant

[†] The current absence of data on resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding MIC/zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

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.

Quality Control:

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.[1,2,3,4] Standard levofloxacin powder should provide the

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range of MIC values noted in Table 12. For the diffusion technique using the 5 mcg disk, the criteria in Table 12 should be achieved.

Table 12: Quality Control Ranges for Susceptibility Testing

Microorganism	Microorganism QC Number	MIC (mcg/mL)	Disk Diffusion (zone diameter in mm)
Enterococcus faecalis	ATCC 29212	0.25 – 2	--
Escherichia coli	ATCC 25922	0.008 – 0.06	29 – 37
Escherichia coli	ATCC 35218	0.015 – 0.06	--
Haemophilus influenzae	ATCC 49247	0.008 – 0.03	32 – 40
Pseudomonas aeruginosa	ATCC 27853	0.5 – 4	19 – 26
Staphylococcus aureus	ATCC 29213	0.06 – 0.5	--
Staphylococcus aureus	ATCC 25923	--	25 – 30
Streptococcus pneumoniae	ATCC 49619	0.5 – 2	20 – 25

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 mcg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of LEVAQUIN® averaged approximately 11.8 mcg/g at C_{max}.

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

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

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13.2 Animal Toxicology and/or Pharmacology

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested *[see Warnings and Precautions (5.10)]*. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (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 (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels.

When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While 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.

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

In dogs, levofloxacin administered at 6 mg/kg or higher by rapid intravenous injection produced hypotensive effects. These effects were considered to be related to histamine release.

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.

14 CLINICAL STUDIES

14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous LEVAQUIN® (750 mg once daily) followed by oral LEVAQUIN® (750 mg once daily) for a total of 7–15 days to intravenous imipenem/cilastatin (500–1000 mg every 6–8 hours daily) followed by oral

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ciprofloxacin (750 mg every 12 hours daily) for a total of 7–15 days. LEVAQUIN®-treated patients received an average of 7 days of intravenous therapy (range: 1–16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1–19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the LEVAQUIN® arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the LEVAQUIN® arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented *Pseudomonas aeruginosa* infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the LEVAQUIN® arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the LEVAQUIN® arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection.

Clinical success rates in clinically and microbiologically evaluable patients at the posttherapy visit (primary study endpoint assessed on day 3–15 after completing therapy) were 58.1% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the posttherapy visit were 66.7% for LEVAQUIN® and 60.6% for comparator. The 95% CI for the difference of eradication rates (LEVAQUIN® minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen are detailed in Table 13.

Table 13: Clinical Success Rates and Bacteriological Eradication Rates (Nosocomial Pneumonia)

Pathogen	**N**	**LEVAQUIN® No. (%) of Patients Microbiologic/ Clinical Outcomes**	**N**	**Imipenem/Cilastatin No. (%) of Patients Microbiologic/ Clinical Outcomes**
MSSA*	21	14 (66.7)/13 (61.9)	19	13 (68.4)/15 (78.9)
P. aeruginosa†	17	10 (58.8)/11 (64.7)	17	5 (29.4)/7 (41.2)
S. marcescens	11	9 (81.8)/7 (63.6)	7	2 (28.6)/3 (42.9)
E. coli	12	10 (83.3)/7 (58.3)	11	7 (63.6)/8 (72.7)
K. pneumoniae‡	11	9 (81.8)/5 (45.5)	7	6 (85.7)/3 (42.9)
H. influenzae	16	13 (81.3)/10 (62.5)	15	14 (93.3)/11 (73.3)
S. pneumoniae	4	3 (75.0)/3 (75.0)	7	5 (71.4)/4 (57.1)

* Methicillin-susceptible *S. aureus*

† See above text for use of combination therapy

‡ The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study

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14.2 Community-Acquired Pneumonia: 7–14 day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing LEVAQUIN® 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with LEVAQUIN® at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (LEVAQUIN® minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg LEVAQUIN® administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies are presented in Table 14.

Table 14: Bacteriological Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

Pathogen	No. Pathogens	Bacteriological Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100.0

Community-Acquired Pneumonia Due to Multi-Drug Resistant *Streptococcus pneumoniae*

LEVAQUIN® was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* (MDRSP). MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 15.

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Table 15: Clinical and Bacterial Success Rates for LEVAQUIN®-Treated MDRSP in Community Acquired Pneumonia Patients (Population Valid for Efficacy)

Screening Susceptibility	Clinical Success		Bacteriological Success*	
	n/N†	%	n/N‡	%
Penicillin-resistant	16/17	94.1	16/17	94.1
2nd generation Cephalosporin resistant	31/32	96.9	31/32	96.9
Macrolide-resistant	28/29	96.6	28/29	96.6
Trimethoprim/ Sulfamethoxazole resistant	17/19	89.5	17/19	89.5
Tetracycline-resistant	12/12	100	12/12	100

* One patient had a respiratory isolate that was resistant to tetracycline, cefuroxime, macrolides and TMP/SMX and intermediate to penicillin and a blood isolate that was intermediate to penicillin and cefuroxime and resistant to the other classes. The patient is included in the database based on respiratory isolate.

† n=the number of microbiologically evaluable patients who were clinical successes; N=number of microbiologically evaluable patients in the designated resistance group.

‡ n=the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N=number of MDRSP isolates in a designated resistance group.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 16.

Table 16: Clinical Success and Bacteriologic Eradication Rates for Resistant *Streptococcus pneumoniae* (Community Acquired Pneumonia)

Type of Resistance	Clinical Success	Bacteriologic Eradication
Resistant to 2 antibacterials	17/18 (94.4%)	17/18 (94.4%)
Resistant to 3 antibacterials	14/15 (93.3%)	14/15 (93.3%)
Resistant to 4 antibacterials	7/7 (100%)	7/7 (100%)
Resistant to 5 antibacterials	0	0
Bacteremia with MDRSP	8/9 (89%)	8/9 (89%)

14.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg, IV or orally, every day for five days or LEVAQUIN® 500 mg IV or orally, every day for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the LEVAQUIN® 750 mg group and 91.1% in the LEVAQUIN® 500 mg group. The 95% CI for the difference of response rates (LEVAQUIN® 750 minus LEVAQUIN® 500) was [-5.9, 5.4]. In the clinically evaluable population (31–38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the LEVAQUIN® 750 mg group and 2 out of 147 patients in the LEVAQUIN® 500 mg group. Given the small numbers observed, the significance of this

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finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in Table 17.

Table 17: Bacteriological Eradication Rates (Community-Acquired Pneumonia)

S. pneumoniae	19/20 (95%)
Haemophilus influenzae	12/12 (100%)
Haemophilus parainfluenzae	10/10 (100%)
Mycoplasma pneumoniae	26/27 (96%)
Chlamydophila pneumoniae	13/15 (87%)

14.4 Acute Bacterial Sinusitis: 5-day and 10–14 day Treatment Regimens

LEVAQUIN® is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg by mouth × 5 days or 500 mg by mouth once daily × 10–14 days. To evaluate the safety and efficacy of a high dose short course of LEVAQUIN®, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing LEVAQUIN® 750 mg by mouth once daily for five days to LEVAQUIN® 500 mg by mouth once daily for 10 days.

Clinical success rates (defined as complete or partial resolution of the pre-treatment signs and symptoms of ABS to such an extent that no further antibiotic treatment was deemed necessary) in the microbiologically evaluable population were 91.4% (139/152) in the LEVAQUIN® 750 mg group and 88.6% (132/149) in the LEVAQUIN® 500 mg group at the test-of-cure (TOC) visit (95% CI [-4.2, 10.0] for LEVAQUIN® 750 mg minus LEVAQUIN® 500 mg).

Rates of clinical success by pathogen in the microbiologically evaluable population who had specimens obtained by antral tap at study entry showed comparable results for the five- and ten-day regimens at the test-of-cure visit 22 days post treatment.

Table 18: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)

Pathogen	**LEVAQUIN® 750 mg × 5 days**	**LEVAQUIN® 500 mg × 10 days**
*Streptococcus pneumoniae**	25/27 (92.6%)	26/27 (96.3%)
*Haemophilus influenzae**	19/21 (90.5%)	25/27 (92.6%)
*Moraxella catarrhalis**	10/11 (90.9%)	13/13 (100%)

* Note: Forty percent of the subjects in this trial had specimens obtained by sinus endoscopy. The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in the above table.

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14.5 Complicated Skin and Skin Structure Infections

Three hundred ninety-nine patients were enrolled in an open-label, randomized, comparative study for complicated skin and skin structure infections. The patients were randomized to receive either LEVAQUIN® 750 mg once daily (IV followed by oral), or an approved comparator for a median of 10 ± 4.7 days. As is expected in complicated skin and skin structure infections, surgical procedures were performed in the LEVAQUIN® and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the LEVAQUIN®-treated patients and 44% of the comparator-treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2–5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with LEVAQUIN® and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

14.6 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral LEVAQUIN® 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the LEVAQUIN® and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5–18 days after completion of therapy was 75.0% in the LEVAQUIN® group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for LEVAQUIN® minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 19.

Table 19: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

	LEVAQUIN® (N=136)		**Ciprofloxacin (N=125)**	
Pathogen	**N**	**Eradication**	**N**	**Eradication**
E. coli	15	14 (93.3%)	11	9 (81.8%)
E. faecalis	54	39 (72.2%)	44	33 (75.0%)
*S. epidermidis**	11	9 (81.8%)	14	11 (78.6%)

* Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.

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Eradication rates for *S. epidermidis* when found with other co-pathogens are consistent with rates seen in pure isolates.

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–18 days after completion of therapy were 75.0% for LEVAQUIN®-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for LEVAQUIN® minus ciprofloxacin). Clinical long-term success (24–45 days after completion of therapy) rates were 66.7% for the LEVAQUIN®-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for LEVAQUIN® minus ciprofloxacin).

14.7 Complicated Urinary Tract Infections and Acute Pyelonephritis: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of LEVAQUIN®, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing LEVAQUIN® 750 mg IV or orally once daily for 5 days (546 patients) with ciprofloxacin 400 mg IV or 500 mg orally twice daily for 10 days (563 patients). Patients with AP complicated by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of LEVAQUIN® and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 20.

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Table 20: Bacteriological Eradication at Test-of-Cure

	LEVAQUIN® 750 mg orally or IV once daily for 5 days		**Ciprofloxacin** 400 mg IV/500 mg orally twice daily for 10 days		**Overall Difference [95% CI]**
	n/N	%	n/N	%	LEVAQUIN®-Ciprofloxacin
mITT Population*					
Overall (cUTI or AP)	252/333	75.7	239/318	75.2	0.5 (-6.1, 7.1)
cUTI	168/230	73.0	157/213	73.7	
AP	84/103	81.6	82/105	78.1	
Microbiologically Evaluable Population†					
Overall (cUTI or AP)	228/265	86.0	215/241	89.2	-3.2 [-8.9, 2.5]
cUTI	154/185	83.2	144/165	87.3	
AP	74/80	92.5	71/76	93.4	

* The mITT population included patients who received study medication and who had a positive ($\geq 10^5$ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

† The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at $\geq 10^5$ CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to LEVAQUIN® treatment are presented in Table 21.

Table 21: Bacteriological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to LEVAQUIN® 750 mg QD for 5 Days Treatment

Pathogen	**Bacteriological Eradication Rate (n/N)**	**%**
*Escherichia coli**	155/172	90
Klebsiella pneumoniae	20/23	87
Proteus mirabilis	12/12	100

* The predominant organism isolated from patients with AP was *E. coli*: 91% (63/69) eradication in AP and 89% (92/103) in patients with cUTI.

14.8 Complicated Urinary Tract Infections and Acute Pyelonephritis: 10-day Treatment Regimen

To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of LEVAQUIN®, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing LEVAQUIN® 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients

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with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 30% of enrollment. Microbiological efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1–12 days post-therapy in patients with a pathogen identified at baseline.

The bacteriologic cure rates overall for LEVAQUIN® and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 22.

Table 22: Bacteriological Eradication Overall (cUTI or AP) at Test-Of-Cure*

	LEVAQUIN® 250 mg once daily for 10 days		**Ciprofloxacin** 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population†	174/209	83.3	184/219	84.0
Microbiologically Evaluable Population‡	164/177	92.7	159/171	93.0

* 1–9 days posttherapy for 30% of subjects enrolled prior to a protocol amendment; 5–12 days posttherapy for 70% of subjects.

† The mITT population included patients who had a pathogen isolated at baseline. Patients with missing response were counted as failures in this analysis.

‡ The Microbiologically Evaluable population included mITT patients who met protocol-specified evaluability criteria.

14.9 Inhalational Anthrax (Post-Exposure)

The effectiveness of LEVAQUIN® for this indication is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. LEVAQUIN® has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens *[see Indications and Usage (1.13)*; *Dosage and Administration (2.1, 2.2)]*.

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0-24}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily *[see Clinical Pharmacology (12.3)]*.

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In adults, the safety of LEVAQUIN® for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited. Prolonged LEVAQUIN® therapy in adults should only be used when the benefit outweighs the risk.

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendinopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited *[see Warnings and Precautions (5.10), Use in Specific Populations (8.4)]*.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD_{50} (~2.7×10^6) spores (range 17 – 118 LD_{50}) of *B. anthracis* (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 mcg/mL. Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean (SD) steady state $AUC_{0\text{-}24}$ was 33.4 ± 3.2 mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral LEVAQUIN® beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P=0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

14.10 Plague

Efficacy studies of LEVAQUIN® could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals.

The mean plasma concentrations of LEVAQUIN® associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens *[see Indications and Usage (1.14), Dosage and Administration (2.1), (2.2)]*.

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure ($AUC_{0\text{-}24}$) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL,

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respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily *[see Clinical Pharmacology (12.3)]*.

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD_{50} (range 3 to 145 LD_{50}) of *Yersinia pestis* (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the *Y. pestis* strain used in this study was 0.03 mcg/mL. Mean plasma concentrations of levofloxacin achieved at the end of a single 30-min infusion ranged from 2.84 to 3.50 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from <0.03 to 0.06 mcg/mL. Mean (SD) AUC_{0-24} was 11.9 (3.1) mcg.h/mL (range 9.50 to 16.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. LEVAQUIN® or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39°C for more than 1 hour). Mortality in the LEVAQUIN® group was significantly lower (1/17) compared to the placebo group (7/7) [p<0.001, Fisher's Exact Test; exact 95% confidence interval (-99.9%, -55.5%) for the difference in mortality]. One levofloxacin-treated animal was euthanized on Day 9 post-exposure to *Y. pestis* due to a gastric complication; it had a blood culture positive for *Y. pestis* on Day 3 and all subsequent daily blood cultures from Day 4 through Day 7 were negative.

15 REFERENCES

1. Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard – 9th ed. CLSI Document M7-A9, CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA, 2012.

2. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 22nd Informational Supplement. CLSI Document M100 – S22, 2012.

3. CLSI Performance Standards for Antimicrobial Disk Susceptibility Tests. Approved Standard – 11th ed. CLSI M2-A11, 2012.

4. CLSI. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline – 2nd ed. CLSI Document M45-A2, 2010.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 LEVAQUIN® Tablets

LEVAQUIN® Tablets are supplied as 250, 500, and 750 mg capsule-shaped, coated tablets. LEVAQUIN® Tablets are packaged in bottles and in unit-dose blister strips in the following configurations:

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- 250 mg tablets are terra cotta pink and are imprinted: "LEVAQUIN" on one side and "250" on the other side
  - bottles of 50 (NDC 50458-920-50)
  - unit-dose/100 tablets (NDC 50458-920-10)
- 500 mg tablets are peach and are imprinted: "LEVAQUIN" on one side and "500" on the other side
  - bottles of 50 (NDC 50458-925-50)
  - unit-dose/100 tablets (NDC 50458-925-10)
- 750 mg tablets are white and are imprinted "LEVAQUIN" on one side and "750" on the other side
  - bottles of 20 (NDC 50458-930-20)
  - unit-dose/100 tablets (NDC 50458-930-10)

LEVAQUIN® Tablets should be stored at 15° to 30°C (59° to 86°F) in well-closed containers.

LEVAQUIN® Tablets are manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Ortho LLC, Gurabo, Puerto Rico 00778.

16.2 LEVAQUIN® Oral Solution

LEVAQUIN® Oral Solution is supplied in a 16 oz. multi-use bottle (NDC 50458-170-01). Each bottle contains 480 mL of the 25 mg/mL levofloxacin oral solution.

LEVAQUIN® Oral Solution should be stored at 25°C (77°F); excursions permitted to 15° – 30°C (59° to 86°F) [refer to USP controlled room temperature].

LEVAQUIN® Oral Solution is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Pharmaceutica N.V., Beerse, Belgium.

16.3 LEVAQUIN® Injection, Single-Use Vials

LEVAQUIN® Injection is supplied in single-use vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials and 750 mg of levofloxacin in 30 mL vials.

- 25 mg/mL, 20 mL vials (NDC 50458-164-20)
- 25 mg/mL, 30 mL vials (NDC 50458-165-30)

LEVAQUIN® Injection in Single-Use Vials should be stored at controlled room temperature and protected from light.

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LEVAQUIN® Injection in Single-Use Vials is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Janssen Pharmaceutica N.V., Beerse, Belgium.

16.4 LEVAQUIN® Injection Pre-Mixed Solution, Single-Use in Flexible Container

LEVAQUIN® (levofloxacin in 5% dextrose) Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D5W).

- 5 mg/mL (250 mg), 100 mL flexible container, 50 mL fill (NDC 50458-167-01)
- 5 mg/mL (500 mg), 100 mL flexible container, 100 mL fill (NDC 50458-168-01)
- 5 mg/mL (750 mg), 150 mL flexible container, 150 mL fill (NDC 50458-166-01)

LEVAQUIN® Injection Premix in Flexible Containers should be stored at or below 25°C (77°F); however, brief exposure up to 40°C (104°F) does not adversely affect the product. Avoid excessive heat and protect from freezing and light. LEVAQUIN® Injection Premix in Flexible Containers is manufactured for Janssen Pharmaceuticals, Inc., Titusville, NJ 08560 by Hospira, Inc., Austin, TX 78728.

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Medication Guide (17.6)*

17.1 Antibacterial Resistance

Antibacterial drugs including LEVAQUIN® should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When LEVAQUIN® is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by LEVAQUIN® or other antibacterial drugs in the future.

17.2 Administration with Food, Fluids, and Concomitant Medications

Patients should be informed that LEVAQUIN® Tablets may be taken with or without food. LEVAQUIN® Oral Solution should be taken 1 hour before or 2 hours after eating. The tablet and oral solution should be taken at the same time each day.

Patients should drink fluids liberally while taking LEVAQUIN® to avoid formation of a highly concentrated urine and crystal formation in the urine.

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Antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine should be taken at least two hours before or two hours after oral LEVAQUIN® administration.

17.3 Serious and Potentially Serious Adverse Reactions

Patients should be informed of the following serious adverse reactions that have been associated with LEVAQUIN® or other fluoroquinolone use:

- **Tendon Disorders**: Patients should contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue LEVAQUIN® treatment. **The risk of severe tendon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants**.
- **Exacerbation of Myasthenia Gravis:** Patients should inform their physician of any history of myasthenia gravis. Patients should notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions**: Patients should be informed that LEVAQUIN® can cause hypersensitivity reactions, even following the first dose. Patients should discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Hepatotoxicity**: Severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking LEVAQUIN®. Patients should inform their physician and be instructed to discontinue LEVAQUIN® treatment immediately if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.
- **Convulsions**: Convulsions have been reported in patients taking fluoroquinolones, including LEVAQUIN®. Patients should notify their physician before taking this drug if they have a history of convulsions.
- **Neurologic Adverse Effects (e.g., dizziness, lightheadedness, increased intracranial pressure**): Patients should know how they react to LEVAQUIN® before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Patients should notify their physician if persistent headache with or without blurred vision occurs.
- **Diarrhea**: Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last

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dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

- **Peripheral Neuropathies**: Patients should be informed that peripheral neuropathy has been associated with LEVAQUIN® use. Symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should immediately discontinue treatment and contact their physician.
- **Prolongation of the QT Interval**: Patients should inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.
- **Musculoskeletal Disorders in Pediatric Patients:** Parents should inform their child's physician if their child has a history of joint-related problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any tendon or joint-related problems that occur during or following LEVAQUIN® therapy *[see Warnings and Precautions (5.10)* and *Use in Specific Populations (8.4)]*.
- **Photosensitivity/Phototoxicity**: Patients should be advised that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolone antibiotics. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors when taking fluoroquinolones, they should wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn like reaction or skin eruption occurs, patients should contact their physician.

17.4 Drug Interactions with Insulin, Oral Hypoglycemic Agents, and Warfarin

Patients should be informed that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue LEVAQUIN® and consult a physician.

Patients should be informed that concurrent administration of warfarin and LEVAQUIN® has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin, be monitored for evidence of bleeding, and also have their anticoagulation tests closely monitored while taking warfarin concomitantly.

17.5 Plague and Anthrax Studies

Patients given LEVAQUIN® for these conditions should be informed that efficacy studies could not be conducted in humans for ethical and feasibility reasons. Therefore, approval for these conditions was based on efficacy studies conducted in animals.

Active Ingredient Made in Japan

Finished Product Manufactured by:

- Janssen Ortho LLC, Gurabo, Puerto Rico 00778 (for the Tablets).
- Janssen Pharmaceutica N.V., Beerse, Belgium (for the Oral Solution and Injection, Single-Use Vials).
- Hospira, Inc., Austin, TX 78728 (for the Injection Pre-Mixed Solution Single-Use in Flexible Container).

Manufactured for:

- Janssen Pharmaceuticals, Inc., Titusville, NJ 08560.

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17.6 FDA-Approved Medication Guide

MEDICATION GUIDE
LEVAQUIN® [Leave ah kwin]
(levofloxacin)
Tablets

LEVAQUIN® (levofloxacin)
Oral Solution

LEVAQUIN® (levofloxacin) Injection
for Intravenous Use

LEVAQUIN® (levofloxacin in 5% dextrose) Injection
for Intravenous Use

Read this Medication Guide before you start taking LEVAQUIN and each time you get a refill. There may be new information. This Medication Guide does not take

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the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about LEVAQUIN? LEVAQUIN, a fluoroquinolone antibiotic, can cause serious side effects. Some of these serious side effects could result in death.

If you have any of the following serious side effects while you take LEVAQUIN, get medical help right away. Talk with your healthcare provider about whether you should continue to take LEVAQUIN.

1. Tendon rupture or swelling of the tendon (tendinitis).

- **Tendon problems can happen in people of all ages who take LEVAQUIN.** Tendons are tough cords of tissue that connect muscles to bones.

  Some tendon problems include pain, swelling, tears, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon sites.

- The risk of getting tendon problems while you take LEVAQUIN is higher if you:
  - are over 60 years of age
  - are taking steroids (corticosteroids)
  - have had a kidney, heart or lung transplant.
- Tendon problems can happen in people who do not have the above risk factors when they take LEVAQUIN.
- Other reasons that can increase your risk of tendon problems can include:
  - physical activity or exercise
  - kidney failure
  - tendon problems in the past, such as in people with rheumatoid arthritis (RA)

- Call your healthcare provider right away at the first sign of tendon pain, swelling or inflammation. Stop taking LEVAQUIN until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area.

  The most common area of pain and swelling is the Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the risk of tendon rupture with continued use of LEVAQUIN. You may need a different antibiotic that is not a fluoroquinolone to treat your infection.

- Tendon rupture can happen while you are taking or after you have finished taking LEVAQUIN. Tendon ruptures have happened up to several months after people have finished taking their fluoroquinolone.

- Get medical help right away if you get any of the following signs or symptoms of a tendon rupture:

  - hear or feel a snap or pop in a tendon area
  - bruising right after an injury in a tendon area
  - unable to move the affected area or bear weight

2. **Worsening of myasthenia gravis (a problem that causes muscle weakness).** Fluoroquinolones like LEVAQUIN may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

   - See "**What are the possible side effects of LEVAQUIN?**"

What is LEVAQUIN?

LEVAQUIN is a fluoroquinolone antibiotic medicine used in adults age 18 years or older to treat certain infections caused by certain germs called bacteria. These bacterial infections include:

- nosocomial pneumonia
- community-acquired pneumonia

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- acute sinus infection
- acute worsening of chronic bronchitis
- skin infections, complicated and uncomplicated
- chronic prostate infection
- urinary tract infections, complicated and uncomplicated
- acute kidney infection (pyelonephritis)
- inhalational anthrax
- plague

Studies of LEVAQUIN for use in the treatment of plague and anthrax were done in animals only, because plague and anthrax could not be studied in people.

LEVAQUIN is also used to treat children who are 6 months of age or older and may have breathed in anthrax germs, have plague, or been exposed to plague germs.

It is not known if LEVAQUIN is safe and effective in children under 6 months of age.

The safety and effectiveness in children treated with LEVAQUIN for more than 14 days is not known.

Who should not take LEVAQUIN?

Do not take LEVAQUIN if you have ever had a severe allergic reaction to an antibiotic known as a fluoroquinolone, or if you are allergic to levofloxacin or any of the ingredients in LEVAQUIN. See the end of this leaflet for a complete list of ingredients in LEVAQUIN.

What should I tell my healthcare provider before taking LEVAQUIN?

Before you take LEVAQUIN, tell your healthcare provider if you:

- have tendon problems
- have a problem that causes muscle weakness (myasthenia gravis)
- have central nervous system problems such as seizures (epilepsy)

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- have nerve problems
- have or anyone in your family has an irregular heartbeat, especially a condition called “QT prolongation”
- have low blood potassium (hypokalemia)
- have bone problems
- have joint problems including rheumatoid arthritis (RA)
- have kidney problems. You may need a lower dose of LEVAQUIN if your kidneys do not work well.
- have liver problems
- have diabetes or problems with low blood sugar (hypoglycemia)
- are pregnant or plan to become pregnant. It is not known if LEVAQUIN will harm your unborn child.
- are breastfeeding or plan to breastfeed. It is not known if LEVAQUIN passes into your breast milk. You and your healthcare provider should decide if you will take LEVAQUIN or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

LEVAQUIN and other medicines can affect each other causing side effects.

Especially tell your healthcare provider if you take:

- a steroid medicine.
- an anti-psychotic medicine
- a tricyclic antidepressant
- a water pill (diuretic)
- certain medicines may keep LEVAQUIN from working correctly. Take LEVAQUIN Tablets or Oral Solution either 2 hours before or 2 hours after taking these medicines or supplements:

- an antacid, multivitamin, or other medicines or supplements that have magnesium, aluminum, iron, or zinc
- sucralfate (Carafate®)
- didanosine (Videx®,Videx® EC)

- a blood thinner (warfarin, Coumadin, Jantoven)
- an oral anti-diabetes medicine or insulin
- an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take LEVAQUIN or other fluoroquinolones may increase your risk of central nervous system effects and seizures.
- theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)
- a medicine to control your heart rate or rhythm (antiarrhythmics)

Ask your healthcare provider if you are not sure if any of your medicines are listed above.

Know the medicines you take. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

How should I take LEVAQUIN?

- Take LEVAQUIN exactly as your healthcare provider tells you to take it.
- Take LEVAQUIN at about the same time each day.
- Drink plenty of fluids while you take LEVAQUIN.
- LEVAQUIN Tablets can be taken with or without food.
- Take LEVAQUIN Oral Solution 1 hour before or 2 hours after eating.
- If you miss a dose of LEVAQUIN, take it as soon as you remember. Do not take more than 1 dose in 1 day.
- LEVAQUIN for Injection is given by slow intravenous (I.V.) infusion into your vein over 60 or 90 minutes as prescribed by your healthcare provider.

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- Do not skip any doses of LEVAQUIN or stop taking it, even if you begin to feel better, until you finish your prescribed treatment unless:
    - you have tendon problems. See "**What is the most important information I should know about LEVAQUIN?**".
    - you have a serious allergic reaction. See "**What are the possible side effects of LEVAQUIN?**".
    - your healthcare provider tells you to stop taking LEVAQUIN

  Taking all of your LEVAQUIN doses will help make sure that all of the bacteria are killed. Taking all of your LEVAQUIN doses will help you lower the chance that the bacteria will become resistant to LEVAQUIN. If your infection does not get better while you take LEVAQUIN, it may mean that the bacteria causing your infection may be resistant to LEVAQUIN. If your infection does not get better, call your healthcare provider. If your infection does not get better, LEVAQUIN and other similar antibiotic medicines may not work for you in the future.

- If you take too much LEVAQUIN, call your healthcare provider or get medical help right away.

What should I avoid while taking LEVAQUIN?

- LEVAQUIN can make you feel dizzy and lightheaded. Do not drive, operate machinery, or do other activities that require mental alertness or coordination until you know how LEVAQUIN affects you.

- Avoid sunlamps, tanning beds, and try to limit your time in the sun. LEVAQUIN can make your skin sensitive to the sun (photosensitivity) and the light from sunlamps and tanning beds. You could get severe sunburn, blisters or swelling of your skin. If you get any of these symptoms while you take LEVAQUIN, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of LEVAQUIN?

LEVAQUIN can cause serious side effects, including:

- See "**What is the most important information I should know about LEVAQUIN?**"

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- **Serious allergic reactions.**

  Allergic reactions can happen in people taking fluoroquinolones, including LEVAQUIN, even after only 1 dose. Stop taking LEVAQUIN and get emergency medical help right away if you have any of the following symptoms of a severe allergic reaction:

  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness
  - rapid heartbeat
  - faint
  - skin rash

  Skin rash may happen in people taking LEVAQUIN, even after only 1 dose. Stop taking LEVAQUIN at the first sign of a skin rash and call your healthcare provider. Skin rash may be a sign of a more serious reaction to LEVAQUIN.

- **Liver damage (hepatotoxicity)**: Hepatotoxicity can happen in people who take LEVAQUIN. Call your healthcare provider right away if you have unexplained symptoms such as:

  - nausea or vomiting
  - stomach pain
  - fever
  - weakness
  - abdominal pain or tenderness
  - itching
  - unusual tiredness
  - loss of appetite

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- light colored bowel movements
- dark colored urine
- yellowing of your skin or the whites of your eyes

Stop taking LEVAQUIN and tell your healthcare provider right away if you have yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to LEVAQUIN (a liver problem).

- **Central Nervous System Effects**. Seizures have been reported in people who take fluoroquinolone antibiotics including LEVAQUIN. Tell your healthcare provider if you have a history of seizures. Ask your healthcare provider whether taking LEVAQUIN will change your risk of having a seizure.

  Central Nervous System (CNS) side effects may happen as soon as after taking the first dose of LEVAQUIN. Talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

  - seizures
  - hear voices, see things, or sense things that are not there (hallucinations)
  - feel restless
  - tremors
  - feel anxious or nervous
  - confusion
  - depression
  - trouble sleeping
  - nightmares
  - feel lightheaded
  - feel more suspicious (paranoia)

- suicidal thoughts or acts
- a headache that will not go away, with or without blurred vision.

- **Intestine infection (Pseudomembranous colitis)**
  Pseudomembranous colitis can happen with many antibiotics, including LEVAQUIN. Call your healthcare provider right away if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may have stomach cramps and a fever. Pseudomembranous colitis can happen 2 or more months after you have finished your antibiotic.

- **Changes in sensation and nerve damage (Peripheral Neuropathy)**

  Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including LEVAQUIN. Stop LEVAQUIN and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

  - pain
  - burning
  - tingling
  - numbness
  - weakness

  The nerve damage may be permanent.

- **Serious heart rhythm changes (QT prolongation and torsades de pointes)**

  Tell your healthcare provider right away if you have a change in your heart beat (a fast or irregular heartbeat), or if you faint. LEVAQUIN may cause a rare heart problem known as prolongation of the QT interval. This condition can cause an abnormal heartbeat and can be very dangerous. The chances of this happening are higher in people:

  - who are elderly
  - with a family history of prolonged QT interval
  - with low blood potassium (hypokalemia)

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- who take certain medicines to control heart rhythm (antiarrhythmics)

- **Joint Problems**

  Increased chance of problems with joints and tissues around joints in children can happen. Tell your child's healthcare provider if your child has any joint problems during or after treatment with LEVAQUIN.

- **Changes in blood sugar**

  People who take LEVAQUIN and other fluoroquinolone medicines with oral anti-diabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hyperglycemia). Follow your healthcare provider's instructions for how often to check your blood sugar. If you have diabetes and you get low blood sugar while taking LEVAQUIN, stop taking LEVAQUIN and call your healthcare provider right away. Your antibiotic medicine may need to be changed.

- **Sensitivity to sunlight (photosensitivity)**

  See "**What should I avoid while taking LEVAQUIN?**"

  The most common side effects of LEVAQUIN include:

  - nausea
  - headache
  - diarrhea
  - insomnia
  - constipation
  - dizziness

  In children 6 months and older who take LEVAQUIN to treat anthrax disease or plague, vomiting is also common.

  Low blood pressure can happen when LEVAQUIN is given too fast by IV injection. Tell your healthcare provider if you feel dizzy or faint during a treatment with LEVAQUIN Injection.

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LEVAQUIN may cause false-positive urine screening results for opiates when testing is done with some commercially available kits. A positive result should be confirmed using a more specific test.

These are not all the possible side effects of LEVAQUIN. Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store LEVAQUIN?

- Store LEVAQUIN Tablets at 59°F to 86° F (15°C to 30°C).
- Keep LEVAQUIN Tablets in a tightly closed container.
- Store LEVAQUIN Oral Solution at 59°F to 86° F (15°C to 30°C).

Keep LEVAQUIN and all medicines out of the reach of children.

General information about the safe and effective use of LEVAQUIN

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use LEVAQUIN for a condition for which it is not prescribed. Do not give LEVAQUIN to other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about LEVAQUIN. If you would like more information about LEVAQUIN, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about LEVAQUIN that is written for healthcare professionals.

For more information go to www.levaquin.com or call 1-800-526-7736.

What are the ingredients in LEVAQUIN?

LEVAQUIN Tablets, LEVAQUIN Oral Solution, LEVAQUIN Injection in Single-Use Vials and LEVAQUIN Injection Premix in Single-Use Flexible Containers:

Active ingredient: levofloxacin

All LEVAQUIN Tablets: