DISCLAIMER

All labeling reflected on this website is for informational and promotional purposes only. It is not intended to be used by healthcare professionals or patients for the purpose of prescribing or administering these products. Questions regarding the current content of product labeling should be directed to Akorn's Customer Service department at 800.932.5676.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

LEVOFLOXACIN Injection, Solution for Intravenous Use
Initial U.S. Approval: 1996

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

See full prescribing information for complete boxed warning.

- **Fluoroquinolones, including Levofloxacin Injection, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:**
  - **Tendinitis and tendon rupture (5.2)**
  - **Peripheral neuropathy (5.3)**
  - **Central nervous system effects (5.4)**

Discontinue Levofloxacin Injection immediately and avoid the use of fluoroquinolones, including Levofloxacin Injection, in patients who experience any of these serious adverse reactions (5.1)

- **Fluoroquinolones, including Levofloxacin Injection, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid Levofloxacin Injection in patients with a known history of myasthenia gravis [see *Warnings and Precautions (5.5)*].**
- **Because fluoroquinolones, including Levofloxacin Injection, have been associated with serious adverse reactions (5.1-5.14), reserve Levofloxacin Injection for use in patients who have no alternative treatment options for the following indications:**
  - **Uncomplicated urinary tract infection (1.12)**
  - **Acute bacterial exacerbation of chronic bronchitis (1.13)**
  - **Acute bacterial sinusitis (1.14)**

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Levofloxacin Injection and other antibacterial drugs, Levofloxacin Injection should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria. (1.15)

RECENT MAJOR CHANGES

Boxed Warning	06/2016
Indications and Usage (1)	06/2016
Dosage and Administration (2)	06/2016
Warnings and Precautions (5)	06/2016

INDICATIONS AND USAGE

Levofloxacin Injection 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)
- Skin and Skin Structure Infections: Complicated (1.4) and Uncomplicated (1.5)
- Chronic bacterial prostatitis (1.6)
- Inhalational Anthrax, Post-Exposure (1.7)
- Plague (1.8)
- Urinary tract infections: Complicated (1.9, 1.10) and Uncomplicated (1.12)
- Acute Pyelonephritis (1.11)
- Acute Bacterial Exacerbation of Chronic Bronchitis (1.13)
- Acute Bacterial Sinusitis (1.14)

DOSAGE AND ADMINISTRATION

- Dosage in patients with normal renal function (2.1)

Types of Infection	Dose Every 24 hours	Duration (days)
Nosocomial Pneumonia (1.1)	750 mg	7 to 14
Community Acquired Pneumonia (1.2)	500 mg	7 to 14
Community Acquired Pneumonia (1.3)	750 mg	5
Complicated Skin and Skin Structure Infections (SSSI) (1.4)	750 mg	7 to 14
Uncomplicated SSSI (1.5)	500 mg	7 to 10
Chronic Bacterial Prostatitis (1.6)	500 mg	28
Inhalational Anthrax (Post Exposure) (1.7) 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 (1.8) 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
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
Acute Bacterial Exacerbation of Chronic Bronchitis (1.13)	500 mg	7
Acute Bacterial Sinusitis (1.14)	750 mg	5
	500 mg	10 to 14

- Adjust dose for creatinine clearance < 50 mL/min (2.3, 8.6, 12.3).
- IV Injection, Single-dose Vial: Slow IV infusion only, over 60 or 90 minutes depending on dose. Avoid rapid or bolus IV (2.5).
- Dilute single-dose 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	Strength
Injection: single-dose vials for dilution	500 mg in 20 mL 750 mg in 30 mL

CONTRAINDICATIONS

Known hypersensitivity to Levofloxacin Injection or other quinolones (4, 5.7)

WARNINGS AND PRECAUTIONS

- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4, 5.7).
- Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.6).
- Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur (5.8).
- *Clostridium difficile*-associated colitis: evaluate if diarrhea occurs (5.9).
- 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 (5.10, 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 Akorn, Inc. at 1-800-932-5676 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

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 (5.12, 7.3)

USE IN SPECIFIC POPULATIONS

- **Geriatrics:** Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older (5.8, 8.5, 17). May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use (5.2, 8.5, 17). May be more susceptible to prolongation of the QT interval (5.10, 8.5, 17).
- **Pediatrics:** Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more Levofloxacin Injection-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.11, 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) (1.7, 2.2, 8.4, 14.9) and plague (1.8, 2.2, 8.4, 14.10).

See 17 for PATIENT COUNSELING INFORMATION Medication Guide.

Revised: 8/2016

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

- **Fluoroquinolones, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together [see *Warnings and Precautions (5.1)*], including:**
  - **Tendinitis and tendon rupture [see *Warnings and Precautions (5.2)*]**
  - **Peripheral neuropathy [see *Warnings and Precautions (5.3)*]**
  - **Central nervous system effects [see *Warnings and Precautions (5.4)*]**

Discontinue Levofloxacin Injection immediately and avoid the use of fluoroquinolones, including levofloxacin, in patients who experience any of these serious adverse reactions [see *Warnings and Precautions (5.1)*]

- **Fluoroquinolones, including levofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid Levofloxacin Injection in patients with a known history of myasthenia gravis [see *Warnings and Precautions (5.5)*].**
- **Because fluoroquinolones, including levofloxacin, have been associated with serious adverse reactions [see *Warnings and Precautions (5.1-5.14)*], reserve Levofloxacin Injection for use in patients who have no alternative treatment options for the following indications:**
  - **Uncomplicated urinary tract infection [see *Indications and Usage (1.12)*]**
  - **Acute bacterial exacerbation of chronic bronchitis [see *Indications and Usage (1.13)*]**
  - **Acute bacterial sinusitis [see *Indications and Usage (1.14)*].**

1 INDICATIONS AND USAGE

Levofloxacin Injection is 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. Levofloxacin Injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form).

1.1 Nosocomial Pneumonia

Levofloxacin 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- to 14-day Treatment Regimen

Levofloxacin 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

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

1.4 Complicated Skin and Skin Structure Infections

Levofloxacin 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)*].

1.5 Uncomplicated Skin and Skin Structure Infections

Levofloxacin 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.*

1.6 Chronic Bacterial Prostatitis

Levofloxacin 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)*].

1.7 Inhalational Anthrax (Post-Exposure)

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

1.8 Plague

Levofloxacin 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 levofloxacin 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)*].

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

Levofloxacin 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

Levofloxacin 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

Levofloxacin 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

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

Because fluoroquinolones, including levofloxacin, have been associated with serious adverse reactions [see *Warnings and Precautions (5.1-5.15)*] and for some patients uncomplicated urinary tract infection is self-limiting, reserve levofloxacin for treatment of uncomplicated urinary tract infections in patients who have no alternative treatment options.

1.13 Acute Bacterial Exacerbation of Chronic Bronchitis

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

Because fluoroquinolones, including levofloxacin, have been associated with serious adverse reactions [see *Warnings and Precautions (5.1-5.15)*] and for some patients ABECB is self-limiting, reserve levofloxacin for treatment of ABECB in patients who have no alternative treatment options.

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

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

Because fluoroquinolones, including levofloxacin, have been associated with serious adverse reactions [see *Warnings and Precautions (5.1-5.15)*] and for some patients ABS is self-limiting, reserve levofloxacin for treatment of ABS in patients who have no alternative treatment options.

1.15 Usage

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

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 levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Patients with Normal Renal Function

The usual dose of Levofloxacin 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[1]	Dosed Every 24 hours	Duration (days)[2]
Nosocomial Pneumonia	750 mg	7 to 14
Community Acquired Pneumonia[3]	500 mg	7 to 14
Community Acquired Pneumonia[4]	750 mg	5
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7 to 14
Uncomplicated SSSI	500 mg	7 to 10
Chronic Bacterial Prostatitis	500 mg	28
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg[7,8]	500 mg	60[8]
Pediatric patients < 50 kg and ≥ 6 months of age[7,8]	see Table 2 below (2.2)	60[8]
Plague, adult and pediatric patients>50 kg[9]	500 mg	10 to 14
Pediatric patients < 50 kg and ≥ 6 months of age	see Table 2 below (2.2)	10 to 14
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[5]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)[6]	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)	500 mg	7
Acute Bacterial Sinusitis (ABS)	750 mg	5
	500 mg	10 to 14

[1] Due to the designated pathogens [see *Indications and Usage (1)*].
[2] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
[3] Due to methicillin-susceptible S*taphylococcus 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)*].
[4] 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)*].
[5] 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.
[6] 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.*
[7] 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)*].
[8] The safety of Levofloxacin 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 (5.11), Use in Specific Populations (8.4),* and *Clinical Studies (14.9)*]. Prolonged Levofloxacin therapy should only be used when the benefit outweighs the risk.
[9] Drug administration should begin as soon as possible after suspected or confirmed exposure to *Yersinia pestis*. Higher doses of Levofloxacin 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[1]	Dose	Freq. Once every	Duration[2]
Inhalational Anthrax (post-exposure)[3, 4]			
Pediatric patients > 50 kg	500 mg	24 hr	60 days[4]
Pediatric patients < 50 kg and ≥ 6 months of age	8 mg/kg (not to exceed 250 mg per dose)	12 hr	60 days[4]
Plague[5]			
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 hrs	10 to 14 days

[1] Due to *Bacillus anthracis* [see *Indications and Usage (1.7)*] and *Yersinia pestis* [see *Indications and Usage (1.8)*].
[2] Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.
[3] 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)*]
[4] The safety of Levofloxacin 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 (5.11), Use in Specific Populations (8.4)*, and *Clinical Studies (14.9)*]. Prolonged Levofloxacin therapy should only be used when the benefit outweighs the risk.
[5] 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 Levofloxacin 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

Levofloxacin 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

Levofloxacin Injection

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

Hydration for Patients Receiving Levofloxacin Injection

Adequate hydration of patients receiving intravenous levofloxacin 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 (17.3)*].

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 Levofloxacin Injection with other intravenous substances, additives or other medications should not be added to Levofloxacin Injection in Single-dose 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 Levofloxacin Injection with an infusion solution compatible with Levofloxacin Injection and with any other drug(s) administered via this common line.

Levofloxacin Injection in Single-dose Vials

Single-dose vials require dilution prior to administration.

Levofloxacin Injection is supplied in single-dose vials containing a concentrated levofloxacin solution with the equivalent of 500 mg (20 mL vial) or 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 Levofloxacin Injection single-dose 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 Levofloxacin Injection Solution
0.9% Sodium Chloride Injection, USP	4.71
5% Dextrose Injection, USP	4.58
5% Dextrose/0.9% NaCl Injection	4.62
5% Dextrose in Lactated Ringers	4.92
Plasma-Lyte®56/5% Dextrose Injection	5.03
5% Dextrose, 0.45% Sodium Chloride, and 0.15% Potassium Chloride Injection	4.61
Sodium Lactate Injection (M/6)	5.54

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 Levofloxacin Injection Following Dilution*].

Prepare the desired dosage of levofloxacin according to Table 5:

Table 5: Preparation of Levofloxacin Injection 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 Levofloxacin Injection Following Dilution:

Levofloxacin 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.

3 DOSAGE FORMS AND STRENGTHS

LEVOFLOXACIN INJECTION, in Single-dose 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

4 CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials [see *Warnings and Precautions (5.7)*].

5 WARNINGS AND PRECAUTIONS

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

Fluoroquinolones, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting levofloxacin. Patients of any age or without pre-existing risk factors have experienced these adverse reactions [see *Warnings and Precautions (5.2, 5.3, 5.4)*].

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

5.2 Tendinitis and Tendon Rupture

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.2)*]. This adverse reaction most frequently involves the Achilles tendon and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. Tendinitis or tendon rupture can occur within hours or days of starting levofloxacin or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally.

The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Discontinue levofloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug. Avoid levofloxacin in patients who have a history of tendon disorders or tendon rupture [see *Adverse Reactions (6.3)*; *Patient Counseling Information (17.1)*].

5.3 Peripheral Neuropathy

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of peripheral neuropathy. Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Symptoms may occur soon after initiation of levofloxacin and may be irreversible in some patients [see *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1, 6.2)*].

Discontinue levofloxacin immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation. Avoid fluoroquinolones, including levofloxacin, in patients who have previously experienced peripheral neuropathy [see *Adverse Reactions (6), Patient Counseling Information (17.1)*].

5.4 Central Nervous System Effects

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of central nervous system (CNS) effects, including convulsions, toxic psychoses, increased intracranial pressure (including pseudotumor cerebri). Fluoroquinolones may also cause central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, discontinue levofloxacin and institute appropriate measures. As with other fluoroquinolones, levofloxacin should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction) [see *Adverse Reactions (6); Drug Interactions (7.4, 7.5); Patient Counseling Information (17.1)*].

5.5 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis [see *Adverse Reactions (6.3); Patient Counseling Information (17.1)*].

5.6 Other Serious and Sometimes Fatal Reactions

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

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

Discontinue levofloxacin immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures [see *Adverse Reactions (6); Patient Counseling Information (17.1)*].

5.7 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated [see *Adverse Reactions (6); Patient Counseling Information (17.1)*].

5.8 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity [see *Warnings and Precautions (5.6)*]. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see *Adverse Reactions (6); Patient Counseling Information (17.1)*].

5.9 *Clostridium difficile*-Associated Diarrhea

Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *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 (17.1)*].

5.10 Prolongation of the QT Interval

Some fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including levofloxacin. Levofloxacin 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 (17.1)*].

5.11 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Levofloxacin 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 (1.7, 1.8)*]. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin [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)*].

5.12 Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with Levofloxacin Injection, levofloxacin should be discontinued and appropriate therapy should be initiated immediately [see *Adverse Reactions (6.2); Drug Interactions (7.3); Patient Counseling Information (17.4)*].

5.13 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 (17.1)*].

5.14 Development of Drug Resistant Bacteria

Prescribing levofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see *Patient Counseling Information (17.2)*].

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:

- Disabling and Potentially Irreversible Serious Adverse Reactions [see *Warnings and Precautions (5.1)*]
- Tendinitis and Tendon Rupture [see *Warnings and Precautions (5.2)*]
- Peripheral Neuropathy [see *Warnings and Precautions (5.3)*]
- Central Nervous System Effects [see *Warnings and Precautions (5.4)*]
- Exacerbation of Myasthenia Gravis [see *Warnings and Precautions (5.5)*]
- Other Serious and Sometimes Fatal Reactions [see *Warnings and Precautions (5.6)*]
- Hypersensitivity Reactions [see *Warnings and Precautions (5.7)*]
- Hepatotoxicity [see *Warnings and Precautions (5.8)*]
- *Clostridium difficile*-Associated Diarrhea [see *Warnings and Precautions (5.9)*]
- Prolongation of the QT Interval [see *Warnings and Precautions (5.10)*]
- Musculoskeletal Disorders in Pediatric Patients [see *Warnings and Precautions (5.11)*]
- Blood Glucose Disturbances [see *Warnings and Precautions (5.12)*]
- Photosensitivity/Phototoxicity [see *Warnings and Precautions (5.13)*]
- Development of Drug Resistant Bacteria [see *Warnings and Precautions (5.14)*]

Hypotension has been associated with rapid or bolus intravenous infusion of levofloxacin. Levofloxacin 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 levofloxacin. Therefore, adequate hydration of patients receiving levofloxacin 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 levofloxacin in 7,537 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 levofloxacin for a wide variety of infectious diseases [see *Indications and Usage (1)*]. Patients received levofloxacin doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3 to 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 levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of levofloxacin 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 levofloxacin-treated patients and less common adverse reactions, occurring in 0.1 to <1% of Levofloxacin-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.

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

System/Organ Class	Adverse Reaction	% (N=7,537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia[a] [see *Warnings and Precautions (5.4)*]	4
Nervous System Disorders	headache dizziness [see *Warnings and Precautions (5.4)*]	6 3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea [see *Warnings and Precautions (5.7)*]	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 (5.7)*] pruritus	2 1
Reproductive System and Breast Disorders	vaginitis	1[b]
General Disorders and Administration Site Conditions	edema injection site reaction chest pain	1 1 1

[a] N = 7,274 [b] N = 3,758 (women)

Table 7: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin (N=7,537)

System/Organ Class	Adverse Reaction
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia thrombocytopenia granulocytopenia [see *Warnings and Precautions (5.6)*]
Immune System Disorders	allergic reaction [see *Warnings and Precautions (5.6, 5.7)*]
Metabolism and Nutrition Disorders	hyperglycemia hypoglycemia [see *Warnings and Precautions (5.12)*] hyperkalemia
Psychiatric Disorders	anxiety agitation confusion depression hallucination nightmare[a] [see *Warnings and Precautions (5.4)*] sleep disorder[a] anorexia abnormal dreaming[a]
Nervous System Disorders	tremor convulsions [see *Warnings and Precautions (5.4)*] paresthesia [see *Warnings and Precautions (5.3)*] vertigo hypertonia hyperkinesias abnormal gait somnolence[a] syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest palpitation ventricular tachycardia ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis stomatitis pancreatitis esophagitis gastroenteritis glossitis pseudomembraneous/*C. difficile* colitis [see *Warnings and Precautions (5.9)*]
Hepatobiliary Disorders	abnormal hepatic function increased hepatic enzymes increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	urticaria [see *Warnings and Precautions (5.7)*]
Musculoskeletal and Connective Tissue Disorders	arthralgia tendinitis [see *Warning and Precautions (5.2)*] myalgia skeletal pain
Renal and Urinary Disorders	abnormal renal function acute renal failure [see *Warning and Precautions (5.6)*]

[a] N = 7,274

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

6.3 Postmarketing Experience

Table 8 lists adverse reactions that have been identified during post-approval use of levofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 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 (5.6)*] eosinophilia
Immune System Disorders	hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions anaphylactic shock angioneurotic edema serum sickness [see *Warnings and Precautions (5.6, 5.7)*]
Psychiatric Disorders	psychosis paranoia isolated reports of suicide attempt and suicidal ideation [see *Warnings and Precautions (5.4)*]
Nervous System Disorders	exacerbation of myasthenia gravis [see *Warnings and Precautions (5.5)*] anosmia ageusia parosmia dysgeusia peripheral neuropathy (may be irreversible) [see *Warnings and Precautions (5.3)*] isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudotumor cerebri [see *Warnings and Precautions (5.4)*]
Eye Disorders	uveitis vision disturbance, including diplopia visual acuity reduced vision blurred scotoma
Ear and Labyrinth Disorders	hypoacusis tinnitus
Cardiac Disorders	isolated reports of torsade de pointes electrocardiogram QT prolonged [see *Warnings and Precautions (5.10)*] tachycardia
Vascular Disorders	vasodilatation
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis [see *Warnings and Precautions (5.6)*]
Hepatobiliary Disorders	hepatic failure (including fatal cases) hepatitis jaundice [see *Warnings and Precautions (5.6, 5.8)*]
Skin and Subcutaneous Tissue Disorders	bullous eruptions to include: Stevens-Johnson Syndrome toxic epidermal necrolysis erythema multiforme [see *Warnings and Precautions (5.6)*] photosensitivity/phototoxicity reaction [see *Warnings and Precautions (5.13)*] leukocytoclastic vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture [see *Warnings and Precautions (5.2)*] muscle injury, including rupture rhabdomyolysis
Renal and Urinary Disorders	interstitial nephritis [see *Warnings and Precautions (5.6)*]
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

Levofloxacin 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 levofloxacin 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 levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [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 (5.12); 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 levofloxacin, may increase the risk of CNS stimulation and convulsive seizures [see *Warnings and Precautions (5.4)*].

7.5 Theophylline

No significant effect of levofloxacin 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 population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels [see *Warnings and Precautions (5.4)*].

7.6 Cyclosporine

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other fluoroquinolones. Levofloxacin C_{max} and ke were slightly lower while Tmax and t½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

7.7 Digoxin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for Levofloxacin Injection 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 levofloxacin with probenecid or cimetidine compared to levofloxacin alone. However, these changes do not warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

7.9 Interactions with Laboratory or Diagnostic Testing

Some fluoroquinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available immunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary.

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 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. Levofloxacin 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 Levofloxacin Injection, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species [see *Warnings and Precautions (5.11)* and *Animal Toxicology and/or Pharmacology (13.2)*].

Pharmacokinetics following intravenous administration

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)*].

Inhalational Anthrax (Post-Exposure)

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 I*ndications and Usage (1.7), Dosage and Administration (2.2)* and *Clinical Studies (14.9)*].

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 levofloxacin 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 (1.8), 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, 1,534 children (6 months to 16 years of age) were treated with oral and intravenous levofloxacin. Children 6 months to 5 years of age received levofloxacin 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 (1,340 levofloxacin-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 study drug. Children treated with levofloxacin 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	Levofloxacin Injection N = 1,340	Non-Fluoroquinolone[a] N = 893	p-value[b]
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year[c]	46 (3.4%)	16 (1.8%)	p = 0.025

[a] Non-Fluoroquinolone: ceftriaxone, amoxicillin/ clavulanate, clarithromycin
[b] 2-sided Fisher's Exact Test
[c] There were 1,199 levofloxacin-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%) levofloxacin-treated children and most were treated with analgesics. The median time to resolution was 7 days for levofloxacin-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 levofloxacin-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 levofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing levofloxacin to elderly patients, especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [see *Boxed Warning; Warnings and Precautions (5.2);* and *Adverse Reactions (6.3)*].

In phase 3 clinical trials, 1,945 levofloxacin-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 levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin Injection should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see *Warnings and Precautions (5.8)*].

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) [see *Warnings and Precautions (5.10)*].

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 levofloxacin 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

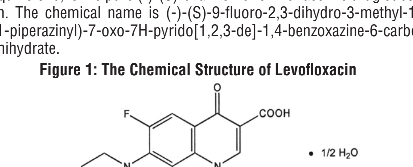
In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1,500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

11 DESCRIPTION

Levofloxacin Injection is a synthetic broad-spectrum antibacterial agent for 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-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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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 levofloxacin 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

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)
500 mg oral single dose tablet, patients with renal insufficiency:							
CLCR 50 to 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 to 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
[2] volume of distribution/bioavailability
[3] healthy males 18 to 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 to 54 years of age
[6] 500 mg every 48h for patients with moderate renal impairment (CLCR 20 to 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 to 75 years of age
[9] healthy females 18 to 80 years of age
[10] young healthy male and female subjects 18 to 36 years of age
[11] healthy elderly male and female subjects 66 to 80 years of age
[12] healthy males and females 19 to 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 levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of Levofloxacin Injection 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.

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 levofloxacin 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, levofloxacin tablets can be administered without regard to food. It is recommended that levofloxacin 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 levofloxacin tablets when equal 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 Levoflaxacin Plasma Concentration vs. Time Profile: 750 mg

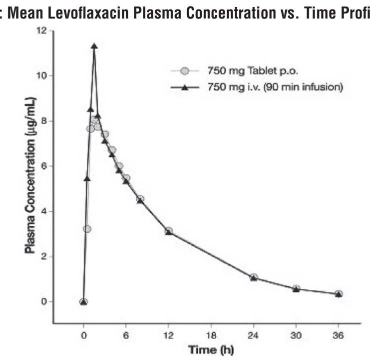
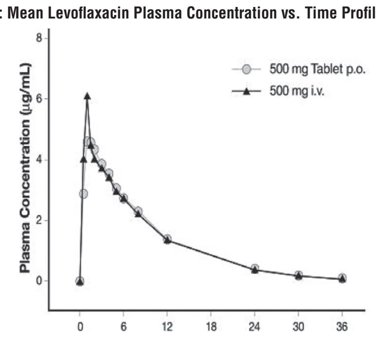


Figure 3: Mean Levoflaxacin Plasma Concentration vs. Time Profile: 500 mg



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 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 levofloxacin, 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 levofloxacin.

Geriatric

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 to 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin Injection 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 levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race

The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 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 levofloxacin from the body, indicating that supplemental doses of levofloxacin 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 levofloxacin 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 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 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]*)
Streptococcus pyogenes

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

Gram-Negative Bacteria

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
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 Levofloxacin Injection in treating clinical infections due to these bacteria have not been established in adequate and well-controlled 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
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:

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 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 to 16	≤13
Enterococcus faecalis	≤2	4	≥8	≥17	14 to 16	≤13
Staphylococcus species	≤2	4	≥8	≥17	14 to 16	≤13
Pseudomonas aeruginosa	≤2	4	≥8	≥17	14 to 16	≤13
Haemophilus influenzae	≤2	--†	--	≥17	--	--
Haemophilus parainfluenzae	≤2	--	--	≥17	--	--
Streptococcus pneumoniae	≤2	4	≥8	≥17	14 to 16	≤13
Streptococcus pyogenes	≤2	4	≥8	≥17	14 to 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 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 to 2	--
Escherichia coli	ATCC 25922	0.008 to 0.06	29 to 37
Escherichia coli	ATCC 35218	0.015 to 0.06	--
Haemophilus influenzae	ATCC 49247	0.008 to 0.03	32 to 40
Pseudomonas aeruginosa	ATCC 27853	0.5 to 4	19 to 26
Staphylococcus aureus	ATCC 29213	0.06 to 0.5	--
Staphylococcus aureus	ATCC 25923	--	25 to 30
Streptococcus pneumoniae	ATCC 49619	0.5 to 2	20 to 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 levofloxacin 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.

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 (5.11)*]. In immature dogs (4 to 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 levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7 to 15 days to intravenous imipenem/cilastatin (500 to 1,000 mg every 6 to 8 hours daily) followed by oral ciprofloxacin (750 mg every 12 hours daily) for a total of 7 to 15 days. Levofloxacin-treated patients received an average of 7 days of intravenous therapy (range: 1 to 16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1 to 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 levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin 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 levofloxacin 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 levofloxacin 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 post-therapy visit (primary study endpoint assessed on day 3 to 15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the post-therapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin 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	Levofloxacin Injection No. (%) of Patients Microbiologic/Clinical Outcomes	N	Imipenem/Cilastatin No. (%) of Patients Microbiologic/Clinical Outcomes
MSSA[a]	21	14 (66.7)/13 (61.9)	19	13 (68.4)/15 (78.9)
P. aeruginosa[b]	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[c]	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)

[a] Methicillin-susceptible *S. aureus*
[b] See above text for use of combination therapy.
[c] The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study.

14.2 Community-Acquired Pneumonia: 7- to 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 levofloxacin 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 post-therapy, and 3 to 4 weeks post-therapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days post-therapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin 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*

Levofloxacin 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.

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

	Clinical Success		Bacteriological Success[a]	
Screening Susceptibility	**n/N[b]**	**%**	**n/N[c]**	**%**
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

[a] 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
[b] .n=the number of microbiologically evaluable patients who were clinical successes; N=number of microbiologically evaluable patients in the designated resistance group.
[c] 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 higher dose and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg, IV or orally, every day for five days or levofloxacin 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 levofloxacin 750 mg group and 91.1% in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-5.9, 5.4]. In the clinically evaluable population (31 to 38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin 750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in 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- to 14-day Treatment Regimens

Levofloxacin is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg by mouth x 5 days or 500 mg by mouth once daily x 10 to 14 days. To evaluate the safety and efficacy of a high dose short course of levofloxacin, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg by mouth once daily for five days to levofloxacin 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 levofloxacin 750 mg group and 88.6% (132/149) in the levofloxacin 500 mg group at the test-of-cure (TOC) visit (95% CI [-4.2, 10.0] for levofloxacin 750 mg minus levofloxacin 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	Levofloxacin Injection 750 mg x 5 days	Levofloxacin Injection 500 mg x 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.

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 levofloxacin 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 levofloxacin and comparator groups. Surgery (incision and drainage or debridement) was performed on 45% of the levofloxacin-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 to 5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin 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 levofloxacin 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 levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5 to 18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 19.

Table 19: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

	Levofloxacin Injection (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.

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 to 18 days after completion of therapy were 75.0% for Levofloxacin Injection-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for Levofloxacin Injection minus ciprofloxacin). Clinical long-term success (24 to 45 days after completion of therapy) rates were 66.7% for the Levofloxacin Injection-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for Levofloxacin Injection 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 levofloxacin, 1,109 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 levofloxacin 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 levofloxacin and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for levofloxacin 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.

Table 20: Bacteriologic Eradication at Test-of-Cure

	Levofloxacin 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	%	Levofloxacin Injection-Ciprofloxacin
mITT Population[a]					
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[b]					
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	

[a] The mITT population included patients who received study medication and who had a positive (≥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.
[b] The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at ≥ 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 levofloxacin treatment are presented in Table 21.

Table 21: Bacteriological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to Levofloxacin 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 levofloxacin, 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 levofloxacin 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients 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 to 12 days post-therapy in patients with a pathogen identified at baseline.

The bacteriologic cure rates overall for levofloxacin 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[a]

	Levofloxacin 250 mg once daily for 10 days		Ciprofloxacin 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population[b]	174/209	83.3	184/219	84.0
Microbiologically Evaluable Population[c]	164/177	92.7	159/171	93.0

[a] 1 to 9 days post-therapy for 30% of subjects enrolled prior to a protocol amendment; 5 to 12 days post-therapy for 70% of subjects.
[b] The mITT population included patients who had a pathogen isolated at baseline. Patients with missing response were counted as failures in this analysis.
[c] The Microbiologically Evaluable population included mITT patients who met protocol-specified evaluability criteria.

14.9 Inhalational Anthrax (Post-Exposure)

The effectiveness of levofloxacin for this indication is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax. The mean plasma concentrations of levofloxacin 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 (1.7); 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)*].

In adults, the safety of levofloxacin for treatment durations of up to 28 days is well characterized. However, information pertaining to extend use at 500 mg daily up to 60 days is limited. Prolonged levofloxacin 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 (5.11), 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 x 10^6) spores (range 17 to 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_{0-24} 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 levofloxacin 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 levofloxacin 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 levofloxacin 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 (1.8), 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)*].

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 strains) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the *Y. pestis* strains used in this study was 0.03 mcg/mL. Mean plasma concentration 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 intravenous levofloxacin or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39°C for more than 1 hour). Mortality in the levofloxacin 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 subsequent daily blood cultures from Day 4 through Day 7 were negative.

15 REFERENCES

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Levofloxacin Injection, Single-dose Vials

Levofloxacin Injection is supplied in single-dose vials. Each vial contains a concentrated solution with the equivalent of 500 mg of levofloxacin in 20 mL vials or 750 mg of levofloxacin in 30 mL vials.

- 25 mg/mL, 20 mL vials (NDC 17478-107-20)
- 25 mg/mL, 30 mL vials (NDC 17478-107-30)

Levofloxacin Injection in Single-dose Vials should be stored at controlled room temperature and protected from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the *FDA-Approved Medication Guide (17.6).*

17.1 Serious Adverse Reactions

Advise patients to stop taking levofloxacin if they experience an adverse reaction and to call their healthcare provider for advice on completing the full course of treatment with another antibacterial drug.

Inform patients of the following serious adverse reactions that have been associated with levofloxacin or other fluoroquinolone use:

- **Disabling and Potentially Irreversible Serious Adverse Reactions That May Occur Together:** Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of levofloxacin and may occur together in the same patient. Inform patients to stop taking levofloxacin immediately if they experience an adverse reaction and to call their healthcare provider.
- **Tendinitis and Tendon Rupture:** Instruct patients to 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 levofloxacin treatment. Symptoms may be irreversible. The risk of severe tendon disorder 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.
- **Peripheral Neuropathies:** Inform patients that peripheral neuropathies have been associated with levofloxacin 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, immediately discontinue levofloxacin and tell them to contact their physician.
- **Central Nervous System Effects** (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including levofloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.
- **Exacerbation of Myasthenia Gravis:** Instruct patients to inform their physician of any history of myasthenia gravis. Instruct patients to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.
- **Hypersensitivity Reactions:** Inform patients that levofloxacin can cause hypersensitivity reactions, even following a single dose, and to 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 (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.
- **Hepatotoxicity:** Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking levofloxacin. Instruct patients to inform their physician 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.
- **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 dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.
- **Prolongation of the QT Interval:** Instruct patients to 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. Instruct patients to notify their physician 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:** Instruct parents to inform their child's physician if the child has a history of joint-related problems before taking this drug. Inform parents of pediatric patients to notify their child's physician of any joint-related problems that occur during or following levofloxacin therapy [see *Warnings and Precautions (5.11)* and *Use in Specific Populations (8.4)*].
- **Photosensitivity/Phototoxicity:** Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Inform patients to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors while using fluoroquinolones, instruct them to 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, instruct patients to contact their physician.

17.2 Antibacterial Resistance

Antibacterial drugs including levofloxacin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When levofloxacin 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 Levofloxacin Injection or other antibacterial drugs in the future.

17.3 Administration with Food, Fluids, and Concomitant Medications

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

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 levofloxacin administration.

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 levofloxacin and consult a physician.

Patients should be informed that concurrent administration of warfarin and levofloxacin 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 levofloxacin 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.

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