

**LEVOFLOXACIN- levofloxacin tablet**  
**LEVOFLOXACIN- levofloxacin tablet, film coated**  
**DIRECT RX**

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**LEVOFLOXACIN**

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

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:

- o Tendinitis and tendon rupture [see Warnings and Precautions (5.2)]

- o Peripheral neuropathy [see Warnings and Precautions (5.3)]

- o Central nervous system effects [see Warnings and Precautions (5.4)]

Discontinue levofloxacin 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 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 to 5.14)], reserve levofloxacin for use in patients who have no alternative treatment options for the following indications:

- o Uncomplicated urinary tract infection [see Indications and Usage (1.12)]
  
- o Acute bacterial exacerbation of chronic bronchitis [see Indications and Usage (1.13)]
  
- o Acute bacterial sinusitis [see Indications and Usage (1.14)].

Levofloxacin tablets are indicated for the treatment of adults ( $\geq 18$  years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed in this section.

### 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  $\beta$ -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  $\geq 2$  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 isolates [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 to 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 (ABS) of chronic bronchitis 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 to 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 to 14 day Treatment Regimens

Levofloxacin is indicated for the treatment of acute bacterial sinusitis (ABS) due to *Streptococcus 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 to 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.

### 2.1 Dosage in Adult Patients with Normal Renal Function

The usual dose of levofloxacin tablets is 250 mg, 500 mg, or 750 mg administered orally

every 24 hours, as indicated by infection and described in Table 1.

These recommendations apply to patients with creatinine clearance  $\geq 50$  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  $\geq 50$  mL/min)

Type of Infection\*

Dosed Every 24 hours

Duration

(days)†

Nosocomial Pneumonia

750 mg

7-14

Community Acquired Pneumonia‡

500 mg

7-14

Community Acquired Pneumonia§

750 mg

5

Complicated Skin and Skin Structure Infections (SSSI)

750 mg

7-14

Uncomplicated SSSI

500 mg

7-10

Chronic Bacterial Prostatitis

500 mg

28

Inhalation Anthrax (Post-Exposure), adult and pediatric patients  $> 50$  kg ¶,§

Pediatric patients  $< 50$  kg and  $\geq 6$  months of age ¶,§

500 mg

see Table 2 below (2.2)

60§

60§

Plague, adult and pediatric patients  $> 50$  kg á

Pediatric patients  $< 50$  kg and  $\geq 6$  months of age

500 mg

see Table 2 below (2.2)

10 to 14

10 to 14

Complicated Urinary Tract Infection (cUTI) or

Acute Pyelonephritis (AP)¶¶

750 mg

5

Complicated Urinary Tract Infection (cUTI) or

Acute Pyelonephritis (AP)#

250 mg

10

Uncomplicated Urinary Tract Infection

250 mg

3

Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)

500 mg

7

Acute Bacterial Sinusitis (ABS)

750 mg

5

500 mg

10-14

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

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

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

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

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

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

PD 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)].

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

á 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  $\geq 6$  months of age is described below in Table 2.

Table 2: Dosage in Pediatric Patients  $\geq 6$  months of age

Type of Infection\*

Dose

Freq. Once every

Duration†

Inhalational Anthrax (post-exposure)‡,§

Pediatric patients  $> 50$  kg

500 mg

24 hr

60 days§

Pediatric patients  $< 50$  kg and  $\geq 6$   
months of age

8 mg/kg

(not to exceed

250 mg per dose)

12 hr

60 days§

Plague¶

Pediatric patients  $> 50$  kg

500 mg

24 hr

10 to 14 days

Pediatric patients  $< 50$  kg and  $\geq 6$   
months of age

8 mg/kg

(not to exceed

250 mg per dose)

12 hr

10 to 14 days

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

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

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

§ The safety of 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 (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)]. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk.



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

### 2.3 Dosage Adjustment in Adults with Renal Impairment

Administer 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  $\geq 50$  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,

#### Levofloxacin Tablets

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

### 2.5 Administration Instructions

#### Food and Levofloxacin Tablets

Levofloxacin tablets can be administered without regard to food.

#### Hydration for Patients Receiving Levofloxacin Tablets

Adequate hydration of patients receiving oral 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 (17.2)].

- Levofloxacin tablets, USP 250 mg are pink colored, capsule shaped, biconvex, film coated tablets debossed with '250n' on one side and 'l' on the other side.
- Levofloxacin tablets, USP 500 mg are orange colored, capsule shaped, biconvex, film coated tablets debossed with '26' on one side and 'l' on the other side.
- Levofloxacin tablets, USP 750 mg are white colored, capsule shaped, biconvex, film coated tablets debossed with '180n' on one side and 'l' on the other side.

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

### 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 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 Tendinopathy 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 (17.3)].

### 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 (17.3)].

### 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 (17.3)].

### 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 (17.3)].

### 5.6 Other Serious and Sometimes Fatal Adverse Reactions

Other serious and sometimes fatal adverse 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 (17.3)].

### 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 (17.3)].

### 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 (17.3)].

### 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 (17.3)].

### 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 (17.3)].

### 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, 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 (17.3)].

### 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 (17.1)].

## 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)]

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 7537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with 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  $\geq 1\%$  of levofloxacin-treated patients and less common adverse reactions, occurring in 0.1 to <1% of levofloxacin-treated patients, are shown in Table 4 and Table 5, respectively. The most common adverse drug reactions ( $\geq 3\%$ ) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

Table 4: Common ( $\geq 1\%$ ) Adverse Reactions Reported in Clinical Trials with Levofloxacin

System/Organ Class	Adverse Reaction	%
(N=7537)		
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia*[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†  
 General Disorders and Administration Site Conditions  
 edema  
 injection site reaction  
 chest pain  
 1  
 1  
 1

\*N = 7274

†N=3758 (women)

Table 5: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin (N=7537)

System/Organ Class

Adverse Reaction

Infections and Infestations

genital moniliasis

Blood and Lymphatic System Disorders



anemiathrombocytopenia  
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\*  
[see Warnings and Precautions (5.4)]  
sleep disorder\*  
anorexia  
abnormal dreaming\*

#### Nervous System Disorders

tremorconvulsions  
[see Warnings and Precautions (5.4)]  
paresthesia [see Warnings and Precautions (5.3)]  
vertigo  
hypertonia  
hyperkinesias  
abnormal gait  
somnolence\*  
syncope

#### Respiratory, Thoracic and Mediastinal Disorders

epistaxis  
Cardiac Disorders

cardiac arrestpalpitation

ventricular tachycardia  
ventricular arrhythmia

#### Vascular Disorders

phlebitis

#### Gastrointestinal Disorders

gastritisstomatitis

pancreatitis

esophagitis

gastroenteritis

glossitis

pseudomembranous/ *C. difficile* colitis [see Warnings and Precautions (5.9)]

#### Hepatobiliary Disorders

abnormal hepatic functionincreased hepatic enzymes

increased alkaline phosphatase

#### Skin and Subcutaneous Tissue Disorders

urticaria [see Warnings and Precautions (5.7)]

#### Musculoskeletal and Connective Tissue Disorders

arthralgiatendinitis

[see Warnings and Precautions (5.2)]

myalgia

skeletal pain

#### Renal and Urinary Disorders

abnormal renal functionacute renal failure [see Warnings and Precautions (5.6)]

\*N = 7274

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

#### 6.3 Postmarketing Experience

Table 6 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 6: 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 (5.2)]  
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 Warning 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

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

### Levofloxacin Tablets

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

## 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<sub>max</sub> and k<sub>e</sub> were slightly lower while T<sub>max</sub> and t<sub>1/2</sub> 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 or digoxin is required when administered concomitantly.

### 7.8 Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the C<sub>max</sub> of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t<sub>1/2</sub> of levofloxacin were higher while CL/F and CLR 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.

### 8.1 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, 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)].

### 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 Indications 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, 1534 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 (1340 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 the 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 7.

Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

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

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

## †2-sided Fisher's Exact Test

‡There were 1199 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  $\geq$  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 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.

In the event of an acute overdose, 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 1500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

[levofloxacinfigure1]

Levofloxacin, USP is a synthetic broad-spectrum antibacterial agent for oral 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, USP

The molecular formula is  $C_{18}H_{20}FN_3O_4 \cdot \frac{1}{2} H_2O$  and the molecular weight is 370.38. Levofloxacin, USP is a light yellowish-white to yellow-white crystals 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, USP is essentially constant (approximately 100 mg/mL). Levofloxacin, USP 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, USP 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 Form

Levofloxacin Tablets, USP are available as film-coated tablets and contain the following inactive ingredients:

- 250 mg: croscarmellose sodium, hypromellose, iron oxide red, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone and titanium dioxide.
- 500 mg: croscarmellose sodium, hypromellose, iron oxide red, iron oxide yellow magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone and titanium dioxide.
- 750 mg: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone and titanium dioxide.

Levofloxacin tablets, USP meets USP Dissolution Test 2.

### 12.1 Mechanism of Action

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

### 12.3 Pharmacokinetics

The mean  $\pm$  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 8.

Table 8: Mean  $\pm$  SD Levofloxacin PK Parameters

Regimen  
C<sub>max</sub>  
(mcg/mL)  
T<sub>max</sub>  
(h)  
AUC (mcg•h/mL)  
CL/F1 (mL/min)  
V<sub>d</sub>/F2 (L)

t<sub>1/2</sub>  
(h)  
CLR(mL/min)  
Single dose  
250 mg oral tablet<sup>3</sup>  
2.8 ± 0.4  
1.6 ± 1  
27.2 ± 3.9  
156 ± 20  
ND  
7.3 ± 0.9  
142 ± 21

500 mg oral tablet<sup>3\*</sup>  
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<sup>12</sup>  
5.8 ± 1.8  
0.8 ± 0.7  
47.8 ± 10.8  
183 ± 40  
112 ± 37.2  
7 ± 1.4  
ND

500 mg IV<sup>3</sup>  
6.2 ± 1  
1 ± 0.1  
48.3 ± 5.4  
175 ± 20  
90 ± 11  
6.4 ± 0.7  
112 ± 25  
750 mg oral tablet<sup>5\*</sup>  
9.3 ± 1.6  
1.6 ± 0.8  
101 ± 20  
129 ± 24  
83 ± 17  
7.5 ± 0.9  
ND

750 mg IV<sup>5</sup>  
11.5 ± 44  
ND

110 ± 40

126 ± 39

75 ± 13

7.5 ± 1.6

ND

Multiple dose

500 mg every 24h oral tablet<sup>3</sup>

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<sup>3</sup>

6.4 ± 0.8

ND

54.6 ± 11.1

158 ± 29

91 ± 12

7 ± 0.8

99 ± 28

500 mg or 250 mg every 24h IV, patients with bacterial infection<sup>6</sup>

8.7 ± 4.7

ND

72.5 ± 51.27

154 ± 72

111 ± 58

ND

ND

750 mg every 24h oral tablet<sup>5</sup>

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<sup>5</sup>

12.1 ± 4.14

ND

108 ± 34

126 ± 37

80 ± 27

7.9 ± 1.9

ND

500 mg oral tablet single dose, effects of gender and age:

Male<sup>8</sup>

5.5 ± 1.1

1.2 ± 0.4

54.4 ± 18.9

166 ± 44

89 ± 13

7.5 ± 2.1

126 ± 38

Female<sup>9</sup>

7 ± 1.6

1.7 ± 0.5

67.7 ± 24.2

136 ± 44

62 ± 16

6.1 ± 0.8

106 ± 40

Young<sup>10</sup>

5.5 ± 1

1.5 ± 0.6

47.5 ± 9.8

182 ± 35

83 ± 18

6 ± 0.9

140 ± 33

Elderly<sup>11</sup>

7 ± 1.6

1.4 ± 0.5

74.7 ± 23.3

121 ± 33

67 ± 19

7.6 ± 2

091 ± 29

500 mg oral single dose tablet, patients with renal insufficiency:

CLCR 50-80 mL/min

7.5 ± 1.8

1.5 ± 0.5

95.6 ± 11.8

88 ± 10

ND

9.1 ± 0.9

57 ± 8

CLCR 20-49 mL/min

7.1 ± 3.1

2.1 ± 1.3

182.1 ± 62.6

51 ± 19

ND

27 ± 10

26 ± 13  
CLCR <20 mL/min  
8.2 ± 2.6  
1.1 ± 1  
263.5 ± 72.5  
33 ± 8  
ND  
35 ± 5  
13 ± 3

Hemodialysis

5.7 ± 1  
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

1clearance/bioavailability

2volume of distribution/bioavailability

3healthy males 18 to 53 years of age

460 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

5healthy male and female subjects 18 to 54 years of age

6500 mg every 48h for patients with moderate renal impairment (CLCR 20 to 50 mL/min) and infections of the respiratory tract or skin

7dose-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

11healthy elderly male and female subjects 66 to 80 years of age

12healthy males and females 19 to 55 years of age.

\*Absolute bioavailability;  $F=0.99 \pm 0.08$  from a 500 mg tablet and  $F=0.99 \pm 0.06$  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 to healthy volunteers, the mean  $\pm$  SD peak plasma concentration attained was  $6.2 \pm 1$  mcg/mL after a 500 mg dose infused over 60 minutes and  $11.5 \pm 4$  mcg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin Oral Solution and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean  $\pm$  SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately  $5.7 \pm 1.4$  and  $0.5 \pm 0.2$  mcg/mL after the 500 mg doses, and  $8.6 \pm 1.9$  and  $1.1 \pm 0.4$  mcg/mL after the 750 mg doses, respectively. The mean  $\pm$  SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately  $6.4 \pm 0.8$  and  $0.6 \pm 0.2$  mcg/mL after the 500 mg doses, and  $12.1 \pm 4.1$  and  $1.3 \pm 0.71$  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 Levofloxacin Plasma Concentration vs. Time Profile: 750 mg

[levofloxacinfigure2]

[levofloxacinfigure2] [levofloxacinfigure2] [levofloxacinfigure2] [levofloxacinfigure2]

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

[levofloxacinfigure3]

[levofloxacinfigure3] 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 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<sub>0 to 24</sub> and C<sub>max</sub>) 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 of Resistance

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

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and  $\beta$ -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]<sup>1</sup>)

Streptococcus pyogenes

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

*Chlamydomyces pneumoniae*

*Mycoplasma pneumoniae*

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

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 ( $\geq 90\%$ ) isolates of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria

*Staphylococcus haemolyticus*

$\beta$ -hemolytic *Streptococcus* (Group C/F)

$\beta$ -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<sup>1,2,4</sup> (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<sup>2,3</sup> requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg levofloxacin to test the susceptibility of bacteria to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according to the criteria outlined in Table 9.

Table 9: Susceptibility Test Interpretive Criteria for Levofloxacin

Minimum Inhibitory Concentrations (mcg/mL)

Disk Diffusion

(zone diameter in mm)

Pathogen

S

I

R

S

I

R

Enterobacteriaceae

≤2

4

≥8

≥17

14-16

≤13

Enterococcus faecalis

≤2

4

≥8

≥17

14-16

≤13

Staphylococcus species

≤2

4

≥8

≥17

14-16

≤13

Pseudomonas aeruginosa

≤2

4

≥8

≥17

14-16

≤13

Haemophilus influenzae

≤2

--†  
 --  
 ≥17  
 --  
 --  
 Haemophilus parainfluenzae  
 ≤2  
 --  
 --  
 ≥17  
 --  
 --  
 Streptococcus pneumoniae  
 ≤2  
 4  
 ≥8  
 ≥17  
 14-16  
 ≤13  
 Streptococcus pyogenes  
 ≤2  
 4  
 ≥8  
 ≥17  
 14-16  
 ≤13  
 Yersinia pestis 4  
 ≤0.25  
 --  
 --  
 --  
 --  
 --  
 Bacillus anthracis4  
 ≤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.<sup>1,2,3,4</sup> Standard levofloxacin powder should provide the range of MIC values noted in Table 10. For the diffusion technique using the 5 mcg disk, the criteria in Table 10 should be achieved.

Table 10: Quality Control Ranges for Susceptibility Testing

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

ATCC 25923

--

25 - 30

*Streptococcus pneumoniae*

ATCC 49619

0.5 - 2

20 - 25

### 13.1 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<sub>max</sub>.

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 Pharmacology & OR Toxicology

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.

#### 14.1 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 1000 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 posttherapy 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]. The microbiological eradication rates at the posttherapy 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 11.

Table 11: Clinical Success Rates and Bacteriological Eradication Rates (Nosocomial Pneumonia)

Pathogen  
N

Levofloxacin  
No. (%) of Patients Microbiologic/ Clinical Outcomes

N  
Imipenem/Cilastatin  
No. (%) of Patients  
Microbiologic/  
Clinical Outcomes  
MSSA\*

21  
14 (66.7)/13 (61.9)

19  
13 (68.4)/15 (78.9)

P. aeruginosa†  
17  
10 (58.8)/11 (64.7)

17  
5 (29.4)/7 (41.2)

S. marcescens  
11  
9 (81.8)/7 (63.6)

7  
2 (28.6)/3 (42.9)

E. coli  
12  
10 (83.3)/7 (58.3)

11  
7 (63.6 )/8 (72.7)

K. pneumoniae ‡  
11  
9 (81.8)/5 (45.5)

7  
6 (85.7)/3 (42.9)

H. influenzae  
16  
13 (81.3)/10 (62.5)

15  
14 (93.3)/11 (73.3)

S. pneumoniae  
4  
3 (75)/3 (75)

7  
5 (71.4)/4 (57.1)

\*Methicillin-susceptible *S. aureus*

†See above text for use of combination therapy

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

## 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 posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, noncomparative 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 *Chlamydomphila pneumoniae*, *Mycoplasma pneumoniae*, and *Legionellapneumophila* were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies are presented in Table 12.

Table 12: Bacteriological Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

Pathogen	No. Pathogens	Bacteriological Eradication Rate (%)
<i>H. influenzae</i>	55	98
<i>S. pneumoniae</i>	83	95
<i>S. aureus</i>	17	88
<i>M. catarrhalis</i>	18	94
<i>H. parainfluenzae</i>	19	95
<i>K. pneumoniae</i>	10	100

#### 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  $\geq 2$  mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP

isolates, 38 patients (95%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 13.

Table 13: Clinical and Bacterial Success Rates for Levofloxacin-Treated MDRSP in Community Acquired Pneumonia Patients (Population Valid for Efficacy)

Screening Susceptibility

Clinical Success

Bacteriological Success\*

n/N†

%

n/N‡

%

Penicillin-resistant

16/17

94.1

16/17

94.1

2nd generation

Cephalosporin resistant

31/32

96.9

31/32

96.9

Macrolide-resistant

28/29

96.6

28/29

96.6

Trimethoprim/Sulfamethoxazole resistant

17/19

89.5

17/19

89.5

Tetracycline-resistant

12/12

100

12/12

100

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

†n=the number of microbiologically evaluable patients who were clinical successes;

N=number of microbiologically evaluable patients in the designated resistance group.

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

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 14.

Table 14: 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 15.

Table 15: Bacteriological Eradication Rates (Community-Acquired Pneumonia)

<i>S. pneumoniae</i>
19/20 (95%)
<i>Haemophilus influenzae</i>
12/12 (100%)
<i>Haemophilus parainfluenzae</i>
10/10 (100%)
<i>Mycoplasma pneumoniae</i>
26/27 (96%)
<i>Chlamydomphila pneumoniae</i>
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] 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 (see Table 16).

Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)

Pathogen

Levofloxacin

750 mg x 5 days

Levofloxacin

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  $10 \pm 4.7$  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 (VB3) 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% 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 17.

Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

Levofloxacin (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%)

*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% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24 to 45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin 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, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing 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 18.

Table 18: Bacteriological 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-	
Ciprofloxacin	
mITT Population*	
Overall (cUTI or AP)	
252/333	
75.7	
239/318	
75.2	
0.5 (-6.1, 7.1)	

cUTI  
168/230  
73  
157/213  
73.7

AP  
84/103  
81.6  
82/105  
78.1

Microbiologically Evaluable Population†  
Overall (cUTI or AP)  
228/265

86  
  
215/241  
  
89.2  
  
-3.2 [-8.9, 2.5]

cUTI  
154/185  
83.2  
144/165  
87.3

AP  
74/80  
92.5  
71/76  
93.4

\*The mITT population included patients who received study medication and who had a positive ( $\geq 105$ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

†The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at  $\geq 105$  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 19.

Table 19: 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 20.

Table 20: Bacteriological Eradication Overall (cUTI or AP) at Test-Of-Cure\*

Levofloxacin

250 mg once daily for 10 days

Ciprofloxacin

500 mg twice daily for 10 days

n/N

%

n/N

%

mITT Population†

174/209

83.3

184/219

84

Microbiologically Evaluable Population‡

164/177

92.7

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

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

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

#### 14.9 Inhalational Anthrax (Post-Exposure)

The effectiveness of 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 (1.13); Dosage and Administration (2.1, 2.2)]. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean ( $\pm$  SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is  $5.7 \pm 1.4$  and  $6.4 \pm 0.8$  mcg/mL, respectively; and the corresponding total plasma exposure (AUC<sub>0 to 24</sub>) is  $47.5 \pm 6.7$  and  $54.6 \pm 11.1$  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 extended 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 (5.10), Use in Specific Populations (8.4)].

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD<sub>50</sub> (~ $2.7 \times 10^6$ ) spores (range 17 to 118 LD<sub>50</sub>) 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<sub>max</sub> (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<sub>0 to 24</sub> was  $33.4 \pm 3.2$  mcg.h/mL (range 30.4 to 36 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 (1.14), Dosage and Administration (2.1), (2.2)].

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean ( $\pm$  SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is  $5.7 \pm 1.4$  and  $6.4 \pm 0.8$  mcg/mL, respectively; and the corresponding total plasma exposure (AUC<sub>0 to 24</sub>) is  $47.5 \pm 6.7$  and  $54.6 \pm 11.1$  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<sub>50</sub> (range 3 to 145 LD<sub>50</sub>) of *Yersinia pestis* (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the *Y. pestis* strain used in this study was 0.03 mcg/mL. Mean plasma concentrations of levofloxacin achieved at the end of a single 30-min infusion ranged from 2.84 to 3.50 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from <0.03 to 0.06 mcg/mL. Mean (SD) AUC<sub>0 to 24</sub> was 11.9 (3.1) mcg.h/mL (range 9.50 to 16.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. levofloxacin or placebo beginning within 6 hrs of the onset of telemetered fever ( $\geq 39^\circ\text{C}$  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 all subsequent daily blood cultures from Day 4 through Day 7 were negative.

#### 16.1 Levofloxacin Tablets, USP

- Levofloxacin Tablets USP, 250 mg are pink colored, capsule shaped, biconvex, film coated tablets debossed with '25' on one side and 'l' on the other side.
- Levofloxacin Tablets USP, 500 mg are orange colored, capsule shaped, biconvex, film coated tablets debossed with '26' on one side and 'l' on the other side.
- Levofloxacin Tablets USP, 750 mg are white colored, capsule shaped, biconvex, film coated tablets debossed with '18' on one side and 'l' on the other side.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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.
- **Aortic aneurysm and dissection:** Inform patients who have or are at risk for an aortic aneurysm that fluoroquinolones, including levofloxacin, have been associated with a 2-fold increased risk of hospitalization for aortic aneurysm and dissection. Inform patients to seek emergency medical care if they experience sudden chest, stomach, or back pain.

- **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 (5.12) 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.

#### 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 or other antibacterial drugs in the future.

#### Administration with Food, Fluids, and Concomitant Medications

Patients should be informed that levofloxacin tablets may be taken with or without food. The tablets should be taken at the same time each day.

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.

#### 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.

#### 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.

**D**

Mfg For: Cipla USA Inc.  
Miami, FL 33156  
NDC 69097-287-81

Mfg Lot:  
2/2/2018

**LEVOFLOXACIN 750mg 14 Tabs**

Generic For: **LEVAQUIN**  
Each tablet contains Levofloxacin USP, 750mg

Lot# Prod# 440-14  
Packaged and Distributed By: **DIRECT**

Discard After: 07/19  
Alpharetta, GA 30005

**M**

NDC 61919-440-14

Medication should be taken with plenty of water. **May Cause:** dizziness, fainting, fast or pounding heartbeat; diarrhea that is watery or bloody

**RX ONLY-KEEP OUT OF REACH OF CHILDREN**  
Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
Dosage: See package insert. Store between 68-77 degrees F.

LEVOFLOXACIN 750mg NDC 61919-440-14 Lot Exp Date 07/19 Mfg NDC 69097-287-81 14 Ta

LEVOFLOXACIN 750mg NDC 61919-440-14 Lot Exp Date 07/19 Mfg NDC 69097-287-81 14 Ta

LEVOFLOXACIN 750mg NDC 61919-440-14 Lot Exp Date 07/19 Mfg NDC 69097-287-81 14 Ta

LEVOFLOXACIN 750mg NDC 61919-440-14 Lot Exp Date 07/19 Mfg NDC 69097-287-81 14 Ta

Mfg For: Cambier Pharm., Inc.  
Placetalley, NJ 08854  
NDC 31722-722-50

Mfg Lot: LEV17031  
BW 9/15/2017 918130

**D**

**LEVOFLOXACIN**  
**500mg 7 Tabs**

Generic For: **LEVAQUIN**  
\*Each film coated tablet contains 500mg of levofloxacin, USP

Lot# Prod# 426-07  
Packaged and Distributed By: **DIRECT Rx**

Discard After: 05/19  
Alpharetta, GA 30005

ANHNO  
Caution: Federal law prohibits transfer of this drug to any person other than the patient for whom it was prescribed.  
**RX ONLY-KEEP OUT OF REACH OF CHILDREN**  
Dosage: See package insert. Store between 68-77 degrees F

NDC 61919-426-07

Medication should be taken with plenty of water. **May Cause: dizziness, fainting, fast or pounding heartbeat; diarrhea that is watery or bloody**

LEVOFLOXACIN 500mg  
NDC 61919-426-07 7 Ta  
Lot Exp Date 05/19  
Mfg NDC 31722-722-50

LEVOFLOXACIN 500mg  
NDC 61919-426-07 7 Ta  
Lot Exp Date 05/19  
Mfg NDC 31722-722-50

LEVOFLOXACIN 500mg  
NDC 61919-426-07 7 Ta  
Lot Exp Date 05/19  
Mfg NDC 31722-722-50

LEVOFLOXACIN 500mg  
NDC 61919-426-07 7 Ta  
Lot Exp Date 05/19  
Mfg NDC 31722-722-50

NDC 61919-426-10

**Levofloxacin**

**500mg 10 Tabs**

Generic For: **Levaquin**  
Each film-coated tablet contains 500 mg of levofloxacin, USP

Lot# 26JY2222  
Prod# 4218-500-10  
Packaged and Distributed By: **DIRECT Rx**

Discard After: 10/31/23  
61919-426-10  
26JY2222 Dawsonville, GA 30534  
10/31/23  
8N5VB

Mfg. For Cambier Pharmaceuticals, Inc.  
Placetalley, NJ 08854  
NDC 31722-722-50

Mfg Lot: LEV21038  
TR 3/28/2022 8434858

Levofloxacin 500mg  
NDC 61919-426-10 10 Tabs  
Lot 26JY2222 Exp 10/31/23  
Mfg NDC 31722-722-50

Levofloxacin 500mg  
NDC 61919-426-10 10 Tabs  
Lot 26JY2222 Exp 10/31/23  
Mfg NDC 31722-722-50

Levofloxacin 500mg  
NDC 61919-426-10 10 Tabs  
Lot 26JY2222 Exp 10/31/23  
Mfg NDC 31722-722-50

Levofloxacin 500mg  
NDC 61919-426-10 10 Tabs  
Lot 26JY2222 Exp 10/31/23  
Mfg NDC 31722-722-50

## LEVOFLOXACIN

levofloxacin tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61919-440(NDC:69097-287)
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LEVOFLOXACIN</b> (UNII: 6GNT3Y5LMF) (LEVOFLOXACIN ANHYDROUS - UNII: RIX4E89Y14)	LEVOFLOXACIN ANHYDROUS	750 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>CROSCARMELOSE SODIUM</b> (UNII: M28OL1HH48)	
<b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ05DW1A)	

<b>POVIDONE</b> (UNII: FZ989GH94E)	
<b>STARCH, CORN</b> (UNII: O8232NY3SJ)	
<b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	

### Product Characteristics

<b>Color</b>	white	<b>Score</b>	no score
<b>Shape</b>	OVAL	<b>Size</b>	20mm
<b>Flavor</b>		<b>Imprint Code</b>	750;C287
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-440-14	14 in 1 BOTTLE; Type 0: Not a Combination Product	03/15/2018	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076890	03/15/2018	

## LEVOFLOXACIN

levofloxacin tablet, film coated

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:61919-426(NDC:31722-722)
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
<b>LEVOFLOXACIN</b> (UNII: 6GNT3Y5LMF) (LEVOFLOXACIN ANHYDROUS - UNII:RIX4E89Y14)	LEVOFLOXACIN ANHYDROUS	500 mg

### Inactive Ingredients

Ingredient Name	Strength
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ0SDW1A)	
<b>POVIDONE</b> (UNII: FZ989GH94E)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>FERRIC OXIDE RED</b> (UNII: 1K09F3G675)	
<b>FERRIC OXIDE YELLOW</b> (UNII: EX438O2MRT)	

<b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)	
<b>CROSCARMELLOSE SODIUM</b> (UNII: M28OL1HH48)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I3O)	
<b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U)	
<b>POLYSORBATE 80</b> (UNII: 6OZP39ZG8H)	

### Product Characteristics

<b>Color</b>	orange	<b>Score</b>	no score
<b>Shape</b>	CAPSULE	<b>Size</b>	18mm
<b>Flavor</b>		<b>Imprint Code</b>	I;26
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:61919-426-07	7 in 1 BOTTLE; Type 0: Not a Combination Product	04/24/2019	
2	NDC:61919-426-10	10 in 1 BOTTLE; Type 0: Not a Combination Product	04/24/2019	

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA202801	04/24/2019	

**Labeler** - DIRECT RX (079254320)

**Registrant** - DIRECT RX (079254320)

### Establishment

Name	Address	ID/FEI	Business Operations
DIRECT RX		079254320	repack(61919-440) , relabel(61919-426)

Revised: 4/2023

DIRECT RX