

**BOXED WARNING**

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

See full prescribing information for complete boxed warning.

Fluoroquinolones, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together [see Warnings and Precautions (5.1)], including:

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

Peripheral neuropathy [see Warnings and Precautions (5.3)]

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

Discontinue levofloxacin 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 (5.1-5.14), reserve levofloxacin for use in patients who have no alternative treatment options for the following indications:

Double click here to open Word Application.

Write unordered list in to word document.

Close Word Application.

Double click here to open Word Application.

Write ordered list in to word document.

Close Word Application.

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

LEVOFLOXACIN tablets, for oral use

Initial U.S. Approval: 1996

**WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS**  
**SEE FULL PRESCRIBING INFORMATION FOR COMPLETE BOXED WARNING.**

Fluoroquinolones, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together (5.1), including:

Tendinitis and tendon rupture (5.2)

Peripheral neuropathy (5.3)

Central nervous system effects (5.4)

Discontinue levofloxacin immediately and avoid the use of fluoroquinolones, including levofloxacin, in patients who experience any of these serious adverse reactions (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 (5.1-5.14), reserve levofloxacin for use in patients who have no alternative treatment options for the following indications:

Uncomplicated urinary tract infection (1.12)

Acute bacterial exacerbation of chronic bronchitis (1.13)

Acute bacterial sinusitis (1.14)

**RECENT MAJOR CHANGES**

Boxed Warning 6/2016

Indications and Usage (1) 6/2016

Dosage and Administration (2) 6/2016

Warnings and Precautions (5) 6/2016

## INDICATIONS AND USAGE

Levofloxacin is a fluoroquinolone antibacterial indicated in adults ( $\geq 18$  years of age) with infections caused by designated, susceptible bacteria (1, 12.4).

Pneumonia: Nosocomial (1.1) and Community Acquired (1.2, 1.3)

Skin and Skin Structure Infections: Complicated (1.4) and Uncomplicated (1.5)

Chronic bacterial prostatitis (1.6)

Inhalational Anthrax, Post-Exposure (1.7)

Plague (1.8)

Urinary Tract Infections: Complicated (1.9, 1.10) and Uncomplicated (1.12)

Acute Pyelonephritis (1.11)

Acute Bacterial Exacerbation of Chronic Bronchitis (1.13)

Acute Bacterial Sinusitis (1.14)

## Usage

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

## DOSAGE AND ADMINISTRATION

Dosage in patients with normal renal function (2.1)

Type of Infection

Dose Every 24 hours

Duration (days)

Nosocomial Pneumonia

(1.1)

750mg

7-14

Community Acquired Pneumonia

(1.2)

500mg

7-14

Community Acquired Pneumonia

(1.3)

750mg

5

Complicated Skin and Skin Structure

Infections (SSSI) (1.4)

750mg

7-14

Uncomplicated SSSI

(1.5)

500mg

7-10

Chronic Bacterial Prostatitis

(1.6)

500mg

28

Inhalation Anthrax (Post Exposure)

(1.7)

Adults and Pediatric Patients > 50kg

500mg

60

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

8 mg/kg BID

(not to exceed 250

mg/dose)

60

Plague (1.8)

Adults and Pediatric Patients > 50kg

500mg

10 to 14

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

8 mg/kg BID

(not to exceed 250

mg/dose)

10 to 14

Complicated Urinary Tract Infection

(1.9) or Acute

Pyelonephritis (1.11)

750mg

5

Complicated Urinary Tract Infection  
(1.10) or Acute Pyelonephritis (1.11)

250mg

10

Uncomplicated Urinary Tract Infection  
(1.12)

250mg

3

Acute Bacterial Exacerbation of Chronic  
Bronchitis (1.13)

500mg

7

Acute Bacterial Sinusitis  
(1.14)

750mg

5

500mg

10-14

Adjust dose for creatinine clearance < 50 mL/min (2.3,8.6 and 12.3)

#### DOSAGE FORMS AND STRENGTHS

Formulation

(3 )

Strength

Tablets

250 mg, 500 mg, and 750 mg

#### CONTRAINDICATIONS

Known hypersensitivity to levofloxacin or other quinolones (4, 5.7)

#### WARNINGS AND PRECAUTIONS

Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4,5.7)

Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.6)

Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported.

Discontinue immediately if signs and symptoms of hepatitis occur (5.8)

Clostridium difficile -associated colitis: evaluate if diarrhea occurs (5.9)

Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval (5.10,8.5)

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

To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd, at 1-866-604-3268 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

#### ADVERSE REACTIONS

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

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#### DRUG INTERACTIONS

Interacting Drug

Interaction

Multivalent cation-containing

products including antacids,

metal cations or didanosine

Absorption of levofloxacin is decreased

when the tablet formulation is taken within

2 hours of these products. (2.4, 7.1)

Warfarin

Effect may be enhanced. Monitor

prothrombin time, INR, watch for bleeding

(7.2)

Antidiabetic agents

Carefully monitor blood glucose (5.12, 7.3)

#### USE IN SPECIFIC POPULATIONS

Geriatrics: Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older (5.8, 8.5, 17). May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use (5.2, 8.5, 17). May be more susceptible to prolongation of the QT interval (5.10, 8.5, 17)

Pediatrics: Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more levofloxacin treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.11, 8.4, 13.2). Safety in

pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) (1.7, 2.2, 8.4, 14.9) and plague (1.8, 2.2, 8.4, 14.10) .

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

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\*

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## 1 INDICATIONS AND USAGE

Levofloxacin 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: 7-14 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*, *Chlamydia pneumoniae*, *Legionella pneumophila*, or *Mycoplasma pneumoniae* [see Dosage and Administration (2.1) and Clinical Studies (14.2)].

MDRSP isolates are strains 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 *Chlamydia pneumoniae* [see Dosage and Administration (2.1) and Clinical Studies (14.3)]

### 1.4 Complicated Skin and Skin Structure Infections

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

### 1.5 Uncomplicated Skin and Skin Structure Infections

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

### 1.6 Chronic Bacterial Prostatitis

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

### 1.7 Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. The effectiveness of levofloxacin is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of

levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk [see Dosage and Administration (2.1, 2.2) and Clinical Studies (14.9)].

### 1.8 Plague

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

### 1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

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

### 1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen

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

### 1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen

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

### 1.12 Uncomplicated Urinary Tract Infections

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

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

### 1.13 Acute Bacterial Exacerbation of Chronic Bronchitis

Levofloxacin is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) due to methicillin-susceptible *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, or *Moraxella catarrhalis*. [see CLINICAL STUDIES (14.4)]

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

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

Levofloxacin is indicated for the treatment of acute bacterial sinusitis 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 (5.1-5.14)] and for some patients ABECB is self-limiting, reserve levofloxacin for treatment of ABECB in patients who have no alternative treatment options.

### 1.15 Usage

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

#### Culture and susceptibility testing

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

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

## 2 DOSAGE AND ADMINISTRATION

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

The usual dose of levofloxacin 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)

\* 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*, *Chlamydomphila 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 *Chlamydomphila 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* .

Ⓟ 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 adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients [see Warnings and Precautions (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)]. Prolonged 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* . Higher doses of levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

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

Inhalational Anthrax (Post-Exposure), adult and pediatric patients  $> 50$  kg Ⓟ,Ⓡ

500 mg see

60Ⓡ

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

Table 2 below (2.2)

60Ⓡ

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

500 mg see

10 to 14

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

Table 2 below (2.2)

10 to 14

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

## 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

\* 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*.

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

## 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.

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

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

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

Levofloxacin 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)].

### 3 DOSAGE FORMS AND STRENGTHS

TABLETS, Film-coated, capsule-shaped

250 mg Brownish pink tablets, debossed with "250" on one side and "C282" on the other side  
500 mg Yellow tablets, debossed with "500" on one side and "C289" on the other side  
750 mg White tablets, debossed with "750" on one side and "C287" on the other side

### 4 CONTRAINDICATIONS

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

### 5 WARNINGS AND PRECAUTIONS

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

Fluoroquinolones, including levofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). These reactions can occur within hours to weeks after starting levofloxacin. Patients of any age or without preexisting 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 Tendinitis and Tendon Rupture

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of tendinitis and tendon rupture in all ages [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]. This adverse reaction most frequently involves the Achilles tendon and has also been reported with 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 usually 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. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. 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 see 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, and insomnia. Suicidal thoughts, and attempted or completed suicide may also occur, especially in patients with a medical history of depression, or an underlying risk factor for depression. 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 requirements for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid levofloxacin in patient with a known history of myasthenia gravis [See Adverse Reactions (6.3); Patient Counseling Information (17.3)]

## 5.6 Other Serious and Sometimes Fatal Reactions

Other serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with fluoroquinolones, including 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) only for the prevention of inhalational anthrax (post-exposure) [see Indications and Usage (1.13, 1.14)] 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 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 (17.2)].

## 6 ADVERSE REACTIONS

### 6.1 Serious and Otherwise Important Adverse Reactions

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

Disabling and Potentially Irreversible Serious Adverse Reactions [see Warnings and Precautions (5.1)]

Tendinitis and Tendon Rupture [see Warnings and Precautions (5.2)]

Peripheral Neuropathy [see Warnings and Precautions (5.3)]

Central Nervous System Effects [see Warnings and Precautions (5.4)]

Exacerbation of Myasthenia Gravis [see Warnings and Precautions (5.5)]

Other Serious and Sometimes Fatal Reactions [see Warnings and Precautions (5.6)]

Hypersensitivity Reactions [see Warnings and Precautions (5.7)]

Hepatotoxicity [see Warnings and Precautions (5.8)]

Clostridium difficile -Associated Diarrhea [see Warnings and Precautions (5.9)]

Prolongation of the QT Interval [see Warnings and Precautions (5.10)]

Musculoskeletal Disorders in Pediatric Patients [see Warnings and Precautions (5.11)]

Blood Glucose Disturbances [see Warnings and Precautions (5.12)]

Photosensitivity/Phototoxicity [see Warnings and Precautions (5.13)]

Development of Drug Resistant Bacteria [see Warnings and Precautions (5.14)]

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 3-14 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.

Table4:Common( $\geq 1\%$ )AdverseReactionsReportedinClinicalTrialswithLevofloxacin

\*N=7274

†N=3758 (women)

System/Organ Class

Adverse Reaction

%(N=7537)

Infections and Infestations

moniliasis

1

Psychiatric Disorders

insomnia\*

[seeWarningsand Precautions

(5.4)]

4

Nervous System Disorders

headache,

dizziness [seeWarningsand

Precautions (5.4)]

6

3

Respiratory , Thoracic and

Mediastinal Disorders

dyspnea

[seeWarningsandPrecautions

(5.7)]

1

Gastrointestinal Disorders

nausea

7

diarrhea

5

constipation

3

abdominal pain

2

vomiting

2

dyspepsia

2

Skin and Subcutaneous

Tissue Disorders

rash [seeWarningsandPrecautions(5.7)]

pruritus

2

1

Reproductive System and

Breast Disorders

vaginitis

1†

General Disorders and

Administration Site

Conditions

edema

1

injection site reaction

1

chest pain

1

Table5:LessCommon(0.1to1%)AdverseReactionsReportedinClinicalTrialswithLevofloxacin(N=7537)

\*N=7274

System/Organ Class  
 Adverse Reaction  
 Infections and  
 Infestations  
 genital moniliasis  
 Blood and Lymphatic  
 System Disorders  
 anemia, thrombocytopenia, granulocytopenia  
 [seeWarningsandPrecautions(5.6)]  
 Immune System  
 Disorders  
 allergic reaction  
 [seeWarningsandPrecautions(5.6,5.7)]  
 Metabolism and  
 Nutrition Disorders  
 hyperglycemia, hypoglycemia  
 [seeWarningsandPrecautions(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  
 Tremor, convulsions  
 [seeWarningsandPrecautions(5.4)],  
 paresthesia  
 [seeWarningsandPrecautions(5.3)] ,  
 Vertigo, hypertonia, hyperkinesias, abnormal gait, somnolence\*, syncope  
 Respiratory , Thoracic  
 and Mediastinal  
 Disorders  
 epistaxis  
 Cardiac Disorders  
 cardiac arrest, palpitation, ventricular tachycardia, ventricular arrhythmia  
 Vascular Disorders  
 phlebitis  
 Gastrointestinal  
 Disorders  
 Gastritis, stomatitis, pancreatitis, esophagitis, gastroenteritis, glossitis,  
 pseudomembraneous/ C.difficile colitis  
 [seeWarningsandPrecautions(5.9)]  
 Hepatobiliary  
 Disorders  
 abnormal hepatic function,  
 increased hepatic enzymes,  
 increased alkaline phosphatase,  
 Skin and Subcutaneous  
 Tissue Disorders  
 urticaria  
 [seeWarningsandPrecautions(5.7)]  
 Musculoskeletal and  
 Connective Tissue  
 Disorders  
 arthralgia, tendinitis  
 [seeWarningsandPrecautions(5.2)],  
 Myalgia,  
 skeletal pain  
 Renal and Urinary  
 Disorders  
 abnormal renal function,  
 acute renal failure  
 [seeWarningsandPrecautions(5.6)]

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, it is not always possible to reliably estimating their frequency or establishing a causal relationship to drug exposure.

Table6:PostmarketingReportsofAdverseDrugReactions

System/Organ  
 Class  
 Adverse Reaction  
 Blood and  
 Lymphatic System

Disorders

Pancytopenia,  
aplastic anemia,  
leukopenia,  
hemolytic anemia

[seeWarningsandPrecautions(5.6)] ,  
eosinophilia

Immune System

Disorders

hypersensitivity reactions, sometimes fatal including:

anaphylactic/anaphylactoid reactions,  
anaphylactic shock,  
angioneurotic edema,  
serum sickness

[seeWarningsandPrecautions(5.6,5.7)>]

Psychiatric

Disorders

Psychosis,

Paranoia,

isolated reports of suicidal ideation, suicide attempt and completed suicide

[seeWarningsandPrecautions(5.4)]

Nervous System

Disorders

exacerbation of myasthenia gravis

[seeWarningsandPrecautions(5.5)],

anosmia,

ageusia,

parosmia,

dysgeusia,

peripheral neuropathy (may be irreversible)

[seeWarningsandPrecautions(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

[seeWarnings

andPrecautions(5.10)],

tachycardia

Vascular

Disorders

vasodilatation

Respiratory ,

Thoracic and

Mediastinal

Disorders

isolated reports of allergic pneumonitis

[seeWarningsandPrecautions(5.6),

Hepatobiliary

Disorders

hepatic failure (including fatal cases),

hepatitis,

jaundice,

[seeWarningsand

Precautions(5.6) , (5.8)]

Skin and

Subcutaneous

Tissue Disorders

bullous eruptions to include:

Stevens-Johnson Syndrome,

toxic epidermal necrolysis

Acute Generalized Exanthematous Pustulosis (AGEP)

fixed drug eruptions,

erythema multiforme

[seeWarningsandPrecautions(5.6)],

photosensitivity/phototoxicity reaction [see Warnings and Precautions (5.13)],  
leukocytoclastic vasculitis  
Musculoskeletal  
and Connective  
Tissue Disorders  
tendon rupture,  
[see Warnings and Precautions (5.2)],  
muscle injury, including rupture,  
rhabdomyolysis  
Renal and  
Urinary Disorders  
interstitial nephritis [see Warnings and Precautions (5.6)]  
General Disorders  
and  
Administration  
Site Conditions  
multi-organ failure,  
pyrexia  
Investigations  
prothrombin time prolonged,  
international normalized ratio prolonged,  
muscle enzymes increased

## 7 DRUG INTERACTIONS

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

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 multivitamins 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 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Pregnancy Category C. Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50 mg/kg/day which corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

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

### 8.3 Nursing Mothers

Based on data on other fluoroquinolones and very limited data on levofloxacin, 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.

\*

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.

#### 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

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 (5.8); 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.

### 10 OVERDOSAGE

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

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

### 11 DESCRIPTION

Levofloxacin tablets, USP is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, USP, 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

[Structure]

The empirical 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 crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin, 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 Forms

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

250 mg (as expressed in the anhydrous form): corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Red iron oxide.

500 mg (as expressed in the anhydrous form): corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Yellow iron oxide.

750 mg (as expressed in the anhydrous form): corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, Povidone and titanium dioxide.

## 12 CLINICAL PHARMACOLOGY

### 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

1 clearance/bioavailability

2 volume of distribution/bioavailability

3 healthy males 18-53 years of age

4 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

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

6 500 mg every 48h for patients with moderate renal impairment (CLCR 20-50 mL/min) and infections of the respiratory tract or skin

7 dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

8 healthy males 22-75 years of age

9 healthy females 18-80 years of age

10 young healthy male and female subjects 18-36 years of age

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

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

\*Absolute bioavailability; F=0.99  $\pm$  0.08 from a 500 mg tablet and F=0.99  $\pm$  0.06 from a 750 mg tablet;

ND=not determined

Regimen

C<sub>max</sub>

T<sub>max</sub>

AUC

CL/F\*

V<sub>d</sub>/F†

t<sub>1/2</sub>

CLR

(mcg/mL)

(h)

(mcg·h/mL)

(mL/min)

(L)

(h)

(mL/min)

Single dose

250 mg oral tablet<sup>3</sup>

2.8  $\pm$  0.4

1.6  $\pm$  1.0

27.2  $\pm$  3.9

156  $\pm$  20

ND

7.3  $\pm$  0.9

142  $\pm$  21

500 mg oral tablet<sup>3\*</sup>

5.1  $\pm$  0.8

1.3  $\pm$  0.6

47.9  $\pm$  6.8

178  $\pm$  28

ND

6.3  $\pm$  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  
7.0 ± 1.4  
ND  
500 mg IV<sup>3</sup>  
6.2 ± 1.0  
1.0 ± 0.1  
48.3 ± 5.4  
175 ± 20  
90 ± 11  
6.4 ± 0.7  
112 ± 25  
750 mg oral tablet<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 ± 4.04  
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 ± 0.8  
99 ± 28  
500 mg or 250 mg every 24h IV, patients with bacterial infection <sup>6</sup>  
8.7 ± 4.07  
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

Female9

7.0 ± 1.6

1.7 ± 0.5

67.7 ± 24.2

136 ± 44

62 ± 16

6.1 ± 0.8

106 ± 40

Young 10

5.5 ± 1.0

1.5 ± 0.6

47.5 ± 9.8

182 ± 35

83 ± 18

6.0 ± 0.9

140 ± 33

Elderly 11

7.0 ± 1.6

1.4 ± 0.5

74.7 ± 23.3

121 ± 33

67 ± 19

7.6 ± 2.0

91 ± 29

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

CLCR 50-80 mL/min

7.5 ± 1.8

1.5 ± 0.5

95.6 ± 11.8

88 ± 10

ND

9.1 ± 0.9

57 ± 8

CLCR 20-49 mL/min

7.1 ± 3.1

2.1 ± 1.3

182.1 ± 62.6

51 ± 19

ND

27 ± 10

26 ± 13

CLCR <20 mL/min

8.2 ± 2.6

1.1 ± 1.0

263.5 ± 72.5

33 ± 8

ND

35 ± 5

13 ± 3

Hemodialysis

5.7 ± 1.0

2.8 ± 2.2

ND

ND

ND

76 ± 42

ND

CAPD

6.9 ± 2.3

1.4 ± 1.1

ND

ND

ND

51 ± 24

ND

#### 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 ± SD peak

plasma concentration attained was  $6.2 \pm 1.0$  mcg/mL after a 500 mg dose infused over 60 minutes and  $11.5 \pm 4.0$  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: 750mg

[Figure01]

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

[Figure 02]

#### 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 - 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>0-24</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 is 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 strains [MDRSP]<sup>1</sup>)

*Streptococcus pyogenes*

<sup>1</sup> 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.

#### **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**

*Chlamydia pneumoniae*

*Mycoplasma pneumoniae*

The following in vitro data are available, but their clinical significance is unknown: Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most ( $\geq 90\%$ ) 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 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 9.

**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**

†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.

**Minimum Inhibitory Concentrations (mcg/mL)**

**Disk Diffusion**

**(zone diameter in mm)**

**Pathogen**

**S**

**I**

**R**

**S**

**I**

**R**

**Enterobacteriaceae**

$\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Enterococcus faecalis**  
 $\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Staphylococcus species**  
 $\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Pseudomonas aeruginosa**  
 $\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Haemophilus influenzae**  
 $\leq 2$   
 --†  
 --  
 $\geq 17$   
 --  
 --  
**Haemophilus parainfluenzae**  
 $\leq 2$   
 --  
 --  
 $\geq 17$   
 --  
 --  
**Streptococcus pneumoniae**  
 $\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Streptococcus pyogenes**  
 $\leq 2$   
 4  
 $\geq 8$   
 $\geq 17$   
 14-16  
 $\leq 13$   
**Yersinia pestis**<sup>4</sup>  
 $\leq 0.25$   
 --  
 --  
 --  
 --  
 --  
**Bacillus anthracis**<sup>4</sup>  
 $\leq 0.25$   
 --  
 --  
 --  
 --  
 --

S = Susceptible, I = Intermediate, R = Resistant

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermediate indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where a high dosage of drug can be used. This category also provides a buffer zone which prevents small

uncontrolled technical factors from causing major discrepancies in interpretation. A report of Resistant indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

**Quality Control:**

Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. 1, 2, 3, 4 Standard levofloxacin powder should provide the range of MIC values noted in Table 10. For the diffusion technique using the 5 mcg disk, the criteria in Table 10 should be achieved.

**Table 10: Quality Control for Susceptibility Testing**

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

**13 NONCLINICAL TOXICOLOGY**

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested [see Warnings and Precautions (5.11)]. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels.

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

While crystalluria has been observed in some intravenous rat studies, urinary crystals are not formed in the bladder, being present only after micturition and are not associated with nephrotoxicity.

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

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

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

## 14 CLINICAL STUDIES

### 14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multicenter, randomized, open-label study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7–15 days to intravenous imipenem/cilastatin (500–1000 mg every 6–8 hours daily) followed by oral ciprofloxacin (750 mg every 12 hours daily) for a total of 7–15 days. Levofloxacin-treated patients received an average of 7 days of intravenous therapy (range: 1–16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1–19 days).

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

Clinical success rates in clinically and microbiologically evaluable patients at the post-therapy visit (primary study endpoint assessed on day 3–15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of response rates (Levofloxacin minus comparator) was [-17.2, 12.0]. The microbiological eradication rates at the post-therapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen are detailed in Table 11.

Table11: Clinical Success Rates and Microbiological Eradication Rates (Nosocomial Pneumonia)

\* 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

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 (75.0)/3 (75.0)  
7  
5 (71.4)/4 (57.1)

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

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days post-therapy, and 3 to 4 weeks post-therapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days post-therapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (Levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to Chlamydia pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila 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 (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis		

18  
 94  
 H. parainfluenzae  
 19  
 95  
 K. pneumoniae  
 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 (95.0%) 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)

\*  
 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.

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

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 the 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 (31–38 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)

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

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

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

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

Rates of clinical success by pathogen in the microbiologically evaluable population who had specimens obtained by antral tap at study entry showed comparable results for the five- and ten-day regimens at the test-of-cure visit 22 days post treatment (see Table 16).

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

\*

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.

Pathogen  
 Levofloxacin  
 750 mg × 5 days  
 Levofloxacin  
 500 mg × 10 days  
*Streptococcus pneumoniae*\*  
 25/27 (92.6%)

26/27 (96.3%)  
 Haemophilus influenzae\*  
 19/21 (90.5%)  
 25/27 (92.6%)  
 Moraxella catarrhalis\*  
 10/11 (90.9%)  
 13/13 (100%)

#### 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 2–5 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 5–18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 17.

Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

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

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 (75.0%)
S. epidermidis*
11
9 (81.8%)
14
11 (78.6%)

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

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24–45 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: Bacteriologic Eradication at Test-of-Cure

\*

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

†

The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at  $\geq 10$  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).

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	
73.0	
157/213	
73.7	
AP	
84/103	
81.6	
82/105	
78.1	
Microbiologically Evaluable Population†	
Overall	
(cUTI or AP)	
228/265	
86.0	
215/241	
89.2	
-3.2 [-8.9, 2.5]	
cUTI	
154/185	
83.2	
144/165	

87.3  
AP  
74/80  
92.5  
71/76  
93.4

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.

Table19:BacteriologicalEradicationRatesforIndividualPathogensRecoveredFromPatientsRandomizedtoLevofloxacin750mgQDfor5DaysTreatment

\*

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.

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

#### 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 1-12 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.

Table20:BacteriologicalEradicationOverall(cUTIorAP)atTest-Of-Cure\*

\*

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

†

1-9 days post-therapy for 30% of subjects enrolled prior to a protocol amendment; 5-12 days post-therapy 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.

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  
84.0  
Microbiologically  
Evaluable Population‡  
164/177  
92.7

#### 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>0-24</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 × 10<sup>6</sup>) spores (range 17 – 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>0-24</sub> was  $33.4 \pm 3.2$  mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P=0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

#### 14.10 Plague

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

The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [see Indications and Usage (1.14), 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>0-24</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>0-24</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.

## 15 REFERENCES

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3. CLSI Performance Standards for Antimicrobial Disk Susceptibility Tests. Approved Standard - 11th ed. CLSI M2-A11, 2012.
4. CLSI. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline - 2nd ed. CLSI Document M45-A2, 2010.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 Levofloxacin Tablets, USP

Levofloxacin tablets, USP

Levofloxacin tablets, USP are supplied as 250, 500, and 750 mg oval-shaped, coated tablets. Levofloxacin tablets, USP are packaged in bottles and in unit-dose blister strips in the following configurations:

- 250 mg tablets are Brownish-pink, oval, biconvex, film coated tablets, debossed 250 on one side and "C282" on the other side.
  - bottles of 50 Tablets (NDC 69097-282-70)
  - bottles of 100 Tablets (NDC 69097-282-07)
- 500 mg tablets are Yellow, oval, biconvex, film coated tablets, debossed 500 on one side and "C289" on the other side,
  - bottles of 50 Tablets (NDC 69097-289-70)
  - bottles of 100 Tablets (NDC 69097-289-07)
- 750 mg tablets are White, oval, biconvex, film coated tablets, debossed 750 on one side and "C287" on the other side,
  - bottles of 20 Tablets (NDC 69097-287-81)
  - bottles of 100 Tablets (NDC 69097-287-07)

Dispense in a well-closed container as defined in the USP. Use child-resistant closure (as required). Store at 20° - 25°C (68° - 77°F) [See USP Controlled Room Temperature].

## 17 PATIENT COUNSELING INFORMATION

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

### Serious Adverse Reactions

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

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

### Disabling and Potentially Irreversible Serious Adverse Reactions That May Occur

Together : Inform patients that disabling and potentially irreversible serious adverse reactions, including tendinitis and tendon rupture, peripheral neuropathies, and central nervous system effects, have been associated with use of levofloxacin and may occur together in the same patient. Inform patients to stop taking levofloxacin immediately if they experience an adverse reaction and to call their healthcare provider.

Tendinitis and Tendon Rupture: Instruct patients to contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue levofloxacin treatment. Symptoms may be irreversible. The risk of severe tendon disorder with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Peripheral Neuropathies: Inform patients that peripheral neuropathies have been associated with levofloxacin use, symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness and/or weakness develop, immediately discontinue levofloxacin and

tell them to contact their physician.

**Central Nervous System Effects** (for example, convulsions, dizziness, lightheadedness, increased intracranial pressure): Inform patients that convulsions have been reported in patients receiving fluoroquinolones, including levofloxacin. Instruct patients to notify their physician before taking this drug if they have a history of convulsions. Inform patients that they should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Instruct patients to notify their physician if persistent headache with or without blurred vision occurs.

**Exacerbation of Myasthenia Gravis:** Instruct patients to inform their physician of any history of myasthenia gravis. Instruct patients to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties.

**Hypersensitivity Reactions:** Inform patients that levofloxacin can cause hypersensitivity reactions, even following a single dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (for example, swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms of an allergic reaction.

**Hepatotoxicity:** Inform patients that severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking levofloxacin. Instruct patients to inform their physician if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine.

**Diarrhea:** Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, instruct patients to contact their physician as soon as possible.

**Prolongation of the QT Interval:** Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents.

Instruct patients to notify their physician if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

**Musculoskeletal Disorders in Pediatric Patients:** Instruct parents to inform their child's physician if the child has a history of joint-related problems before taking this drug. Inform parents of pediatric patients to notify their child's physician of any joint-related problems that occur during or following levofloxacin therapy [see Warnings and Precautions (5.11) and Use in Specific Populations (8.4)].

**Photosensitivity/Phototoxicity:** Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Inform patients to minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors while using fluoroquinolones, instruct them to wear loose-fitting clothes that protect skin from sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, instruct patients to contact their physician.

#### 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 tablet 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.

Manufactured by:

Cipla Ltd.

Verna Goa, India.

Manufactured for:

Cipla USA, Inc.

9100 S. Dadeland Blvd., Suite 1500

Miami, Florida 33156

Revised: 03/2017

## MEDICATION GUIDE

### MEDICATION GUIDE

#### LEVOFLOXACIN TABLETS, USP

[LEE-voe-FLOX-a-sin]

Read the Medication Guide before you start taking levofloxacin tablets and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about levofloxacin tablets?

Levofloxacin, a fluoroquinolone antibiotic, can cause serious side effects. Some of these serious side effects can happen at the same time and could result in death.

If you have any of the following serious side effects while you take levofloxacin tablets, you should stop taking levofloxacin tablets immediately and get medical help right away.

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

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

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

- The risk of getting tendon problems while you take levofloxacin tablets is higher if you:

- are over 60 years of age

- are taking steroids (corticosteroids)

- have had a kidney, heart or lung transplant.

- Tendon problems can happen in people who do not have the above risk factors when they take levofloxacin tablets.

- Other reasons that can increase your risk of tendon problems can include:

- physical activity or exercise

- kidney failure

- tendon problems in the past, such as in people with rheumatoid arthritis (RA)

- Stop taking levofloxacin tablets immediately and get medical help right away at the first sign of tendon pain, swelling or inflammation. Stop taking levofloxacin tablets, USP until tendinitis or tendon rupture has been ruled out by your healthcare provider. Avoid exercise and using the affected area.

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

- Tendon rupture can happen while you are taking or after you have finished taking levofloxacin tablets. Tendon ruptures can happen within hours or days of taking levofloxacin tablets and have happened up to several months after patients have finished taking their fluoroquinolone.

- Stop taking levofloxacin tablets immediately and get medical help right away if you get any of the following signs or symptoms of a tendon rupture:

- hear or feel a snap or pop in a tendon area

- bruising right after an injury in a tendon area

- unable to move the affected area or bear weight

#### 2. Changes in sensation and possible nerve damage (Peripheral Neuropathy). Damage to

the nerves in arms, hands, legs, or feet can happen in people who take fluoroquinolones, including levofloxacin tablets.

Stop taking levofloxacin tablets immediately and talk to your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- pain
- numbness
- burning
- weakness
- tingling

3. Central Nervous System (CNS) effects. Seizures have been reported in people who take fluoroquinolone antibacterial medicines, including levofloxacin. Tell your healthcare provider if you have a history of seizures before you start taking levofloxacin tablets. CNS side effects may happen as soon as after taking the first dose of levofloxacin tablets. Stop taking levofloxacin tablets immediately and talk to your healthcare provider right away if you get any of these side effects, or other changes in mood or behavior:

- seizures
- trouble sleeping
- hear voices, see things or sense things that are not there (hallucinations)
- nightmare
- feel lightheaded or dizzy
- feel more suspicious (paranoia)
- feel restless
- suicidal thoughts or acts
- tremors
- headaches that will not go away, with or without blurred vision
- feel anxious or nervous
- confusion
- depression

4. Worsening of myasthenia gravis (a problem that causes muscle weakness). Fluoroquinolones like levofloxacin may cause worsening of myasthenia gravis symptoms, including muscle weakness and breathing problems. Tell your healthcare provider if you have a history of myasthenia gravis before you start taking levofloxacin tablets. Call your healthcare provider right away if you have any worsening muscle weakness or breathing problems.

What are levofloxacin tablets?

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

- nosocomial pneumonia
- community-acquired pneumonia
- acute sinus infection
- acute worsening of chronic bronchitis
- skin infections, complicated and uncomplicated
- chronic prostate infection
- urinary tract infections, complicated and uncomplicated
- acute kidney infection (pyelonephritis)
- inhalation anthrax
- plague

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

Levofloxacin tablets should not be used in patients with uncomplicated urinary tract infections, acute bacterial exacerbation of chronic bronchitis, or acute bacterial sinusitis if there are other treatment options available.

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

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

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

Who should not take levofloxacin tablets?

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

What should I tell my healthcare provider before taking levofloxacin tablets?

Before you take levofloxacin tablets, tell your healthcare provider if you:

- have tendon problems; levofloxacin tablets should not be used in patients who have a history of tendon problems

have a problem that causes muscle weakness (myasthenia gravis); levofloxacin tablets should not be used in patients who have a known history of myasthenia gravis  
have central nervous system problems such as seizures (epilepsy)  
have nerve problems; levofloxacin tablets should not be used in patients who have a history of a nerve problem called peripheral neuropathy  
have or anyone in your family has an irregular heartbeat, especially a condition called "QT prolongation"  
have low blood potassium (hypokalemia)  
have bone problems  
have joint problems including rheumatoid arthritis (RA)  
have kidney problems. You may need a lower dose of levofloxacin tablets if your kidneys do not work well.  
have liver problems  
have diabetes or problems with low blood sugar (hypoglycemia)  
are pregnant or plan to become pregnant. It is not known if levofloxacin will harm your unborn child.  
are breastfeeding or plan to breastfeed. It is not known if levofloxacin passes into your breast milk. You and your healthcare provider should decide if you will take levofloxacin tablets or breastfeed. You should not do both.

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

Levofloxacin tablets and other medicines can affect each other causing side effects.

Especially tell your healthcare provider if you take:

a steroid medicine.

an anti-psychotic medicine

a tricyclic antidepressant

a water pill (diuretic)

certain medicines may keep levofloxacin tablets from working correctly. Take levofloxacin tablets either 2 hours before or 2 hours after taking these medicines or supplements:

an antacid, multivitamin, or other medicines or supplements that have magnesium, aluminum, iron, or zinc

sucralfate (Carafate®)

didanosine (Videx®, Videx® EC)

a blood thinner (warfarin, Coumadin, Jantoven)

an oral anti-diabetes medicine or insulin

an NSAID (Non-Steroidal Anti-Inflammatory Drug). Many common medicines for pain relief are NSAIDs. Taking an NSAID while you take levofloxacin tablets or other fluoroquinolones may increase your risk of central nervous system effects and seizures.

theophylline (Theo-24®, Elixophyllin®, Theochron®, Uniphyl®, Theolair®)

a medicine to control your heart rate or rhythm (antiarrhythmics)

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

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

How should I take levofloxacin tablets?

Take levofloxacin tablets exactly as prescribed by your healthcare provider tells you to take it.

Take levofloxacin tablets at about the same time each day.

Drink plenty of fluids while taking levofloxacin tablets.

Levofloxacin tablets can be taken with or without food.

If you miss a dose of levofloxacin tablets, take it as soon as you remember. Do not take more than one dose in one day.

Do not skip any doses of levofloxacin tablets, or stop taking it even if you begin to feel better, until you finish your prescribed treatment, unless:

you have tendon problems. See "what is the most important information i should know about levofloxacin tablets?"

you have a serious allergic reaction. See "what are the possible side effects of levofloxacin tablets?"

your healthcare provider tells you to stop taking levofloxacin tablets

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

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

What should I avoid while taking levofloxacin tablets?

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

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

What are the possible side effects of levofloxacin tablets?

Levofloxacin tablets can cause serious side effects including,

See "What Is The Most Important Information I Should Know About levofloxacin tablets?"

- Serious allergic reactions.

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

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

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

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

- nausea or vomiting,
- stomach pain,
- fever,
- weakness,
- abdominal pain or tenderness,
- itching,
- unusual tiredness,
- loss of appetite,
- light colored bowel movements,
- dark colored urine
- yellowing of your skin or the whites of your eyes.

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

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

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

- who are elderly
- with a family history of prolonged QT interval
- with low blood potassium (hypokalemia)
- who take certain medicines to control heart rhythm (antiarrhythmics)

- Joint Problems

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

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

- Sensitivity to sunlight (photosensitivity)

See "what should i avoid while taking levofloxacin tablets?"

The most common side effects of levofloxacin tablets include:

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

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

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

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

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

How should I store levofloxacin tablets?

Store levofloxacin tablets at 20° to 25°C (68°C to 77°C) [See USP Controlled Room Temperature]

Keep levofloxacin tablets and all medicines out of the reach of children.

General Information about about the safe and effective use of levofloxacin tablets, USP

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

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

For more information call Cipla Ltd. at 1-866-604-3268

What are the ingredients in levofloxacin tablets?

- 250 mg levofloxacin film-coated tablets:

- Active ingredient: levofloxacin, USP

- In active ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and red iron oxide

- 500 mg levofloxacin film-coated tablets:

- Active ingredient: levofloxacin, USP

- Inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Yellow iron Oxide.

- 750 mg levofloxacin film-coated tablets:

- Active ingredient: levofloxacin, USP

- Inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone and titanium dioxide.

Manufactured By:

Cipla Ltd.

Verna Goa, India.

Manufactured for:

Cipla USA, Inc.

9100 S. Dadeland Blvd., Suite 1500

Miami, Florida 33156

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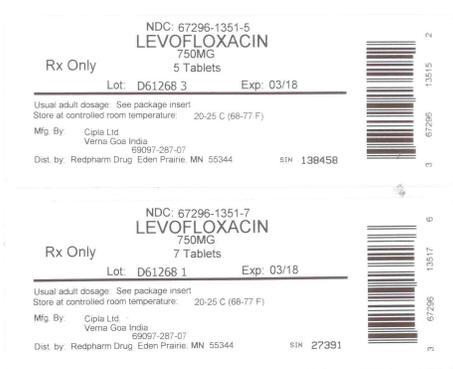
Revised: 3/2017

Summary of Heart Protection Study Results

1 volume of distribution/bioavailability.

\*  
number of patients with indicated event.

### PACKAGE LABEL.PRINCIPAL DISPLAY PANEL



## LEVOFLOXACIN

levofloxacin tablet

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:67296-1351(NDC:69097-287)
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

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

Ingredient Name	Strength
<b>STARCH, CORN</b> (UNII: O8232NY35J)	
<b>MAGNESIUM STEARATE</b> (UNII: 70097M6I30)	
<b>POLYETHYLENE GLYCOL, UNSPECIFIED</b> (UNII: 3WJQ0SDW1A)	
<b>POVIDONE</b> (UNII: FZ989GH94E)	
<b>TITANIUM DIOXIDE</b> (UNII: 15FIX9V2JP)	
<b>CROSCARMELLOSE SODIUM</b> (UNII: M28OL1HH48)	
<b>HYPROMELLOSES</b> (UNII: 3NXW29V3WO)	
<b>CELLULOSE, MICROCRYSTALLINE</b> (UNII: OP1R32D61U)	

**Product Characteristics**

<b>Color</b>	white	<b>Score</b>	no score
<b>Shape</b>	OVAL (Bioconvex)	<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:67296-1351-5	5 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2012	
2	NDC:67296-1351-7	7 in 1 BOTTLE; Type 0: Not a Combination Product	03/30/2012	

**Marketing Information**

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA076890	03/30/2012	

**Labeler - RedPharm Drug, Inc. (828374897)**

**Establishment**

Name	Address	ID/FEI	Business Operations
RedPharm Drug, Inc.		828374897	repack(67296-1351)

Revised: 1/2022

RedPharm Drug, Inc.