**INDICATIONS AND USAGE**

Levofoxacin is a fluoroquinolone antibacterial indicated in adults (18 years of age and older) with infections caused by designated, susceptible bacteria and in pediatric patients where indicated (1.1, 2.1, 2.2).

- Pneumonia: Nosocomial (1.1) and Community Acquired (1.2, 1.3)
- Skin and Skin Structure Infections (SSSI): Complicated (1.4) and Uncomplicated (1.5)
- Chronic bacterial prostatitis (1.6)
- Inhalational Anthrax, Post-Exposure in adult and pediatric patients (1.7)
- Plague in adult and pediatric patients (1.8)
- Urinary Tract Infections (UTI): 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)

**Usual Dosage**

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 in Adult and Pediatric Patients with Creatinine Clearance greater than or equal to 50 mL/minute (2.1, 2.2)**

<table>
<thead>
<tr>
<th>Type of Infection</th>
<th>Dose Every 24 hours</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial Pneumonia (1.1)</td>
<td>750 mg</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Community Acquired Pneumonia (1.2)</td>
<td>500 mg</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Community Acquired Pneumonia (1.3)</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Complicated SSSI (1.4)</td>
<td>750 mg</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Uncomplicated SSSI (1.5)</td>
<td>500 mg every 12 hours</td>
<td>7 to 10</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis (1.6)</td>
<td>500 mg</td>
<td>28</td>
</tr>
<tr>
<td>Inhalational Anthrax (Post-Exposure) (1.7)</td>
<td>500 mg every 12 hours</td>
<td>60</td>
</tr>
<tr>
<td>Adults and Pediatric Patients 50 kg or greater</td>
<td>250 mg every 12 hours</td>
<td>60</td>
</tr>
<tr>
<td>Pediatric Patients 30 kg to less than 50 kg (2.2)</td>
<td>10 to 14</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Plague (1.8)</td>
<td>500 mg every 12 hours</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Adults and Pediatric Patients 50 kg or greater</td>
<td>250 mg</td>
<td>3</td>
</tr>
<tr>
<td>Pediatric Patients 30 kg to less than 50 kg (2.2)</td>
<td>10 to 14</td>
<td>5</td>
</tr>
<tr>
<td>Complicated UTI (1.9) or Acute Pyelonephritis (1.11)</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Complicated UTI (1.10) or Acute Pyelonephritis (1.11)</td>
<td>250 mg</td>
<td>10</td>
</tr>
<tr>
<td>Uncomplicated UTI (1.12)</td>
<td>250 mg</td>
<td>7</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis (1.13)</td>
<td>500 mg</td>
<td>7</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis (1.14)</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis (1.14)</td>
<td>500 mg</td>
<td>10 to 14</td>
</tr>
</tbody>
</table>

- Adjust dose for creatinine clearance less than 50 mL/minute (2.3, 8.6, 12.3)

**CONTRAINDICATIONS**

Known hypersensitivity to levofloxacin or other quinolones (4.5).

- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4.5).
- 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 (5.10).
- 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 (5.11, 8.5).

**ADVERSE REACTIONS**

The most common reactions (≥3%) were nausea, headache, diarrhea, insomnia, constipation and dizziness (6.1).

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

**DRUG INTERACTIONS**

These highlights do not include all the information needed to use LEVOFLOXACIN TABLETS safely and effectively. See full prescribing information for LEVOFLOXACIN TABLETS.
Interacting Drug | Interaction
--- | ---
Multivalent cation-containing products including antacids, metal cations or didanosine | Absorption of levofloxacin is decreased when the tablets are taken within 2 hours of these products. (2.4, 7.1)
Warfarin | Effect may be enhanced. Monitor prothrombin time, INR and watch for bleeding (7.2)
Antidiabetic agents | Carefully monitor blood glucose (5.13, 7.3)

- **Geriatrics:** Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older. They 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. (5.11, 8.5, 17).
- **Pediatrics:** Musculoskeletal disorders (arthritis, arthralgia, tendinopathy, and gait abnormality) seen in more levofloxacin-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.12, 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).
- **Lactation:** Breastfeeding is not recommended during treatment and for an additional 2 days after the last dose. Consider the risks and benefits of continuing breastfeeding.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide. Revised: 12/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

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**FULL PRESCRIBING INFORMATION**

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

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

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

- Fluoroquinolones, including levofloxacin, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis [see Warnings and Precautions (5.5)].
- Because fluoroquinolones, including levofloxacin, have been associated with serious adverse reactions [see Warnings and Precautions (5.1-5.15)], reserve levofloxacin for use in patients who have no alternative treatment options for the following indications:
  - Uncomplicated urinary tract infection [see Indications and Usage (1.12)]
  - Acute bacterial exacerbation of chronic bronchitis [see Indications and Usage (1.13)]
  - Acute bacterial sinusitis [see Indications and Usage (1.14)].

---

**1 INDICATIONS AND USAGE**

**1.1 Nosocomial Pneumonia**

Levofloxacin is indicated in adult patients for the treatment of nosocomial pneumonia due to methicillin-susceptible Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, or Streptococcus pneumoniae. Adjunctive therapy should be used as clinically indicated. Where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended [see Clinical Studies (14.1)].

**1.2 Community-Acquired Pneumonia: 7 to 14 day Treatment Regimen**

Levofloxacin is indicated in adult patients for the treatment of community-acquired pneumonia due to methicillin-susceptible Staphylococcus aureus, Streptococcus
Levofloxacin is indicated in adult patients for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae (excluding multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae (including multi-drug-resistant Streptococcus pneumoniae [MDRSP]), or Chlamydophila pneumoniae (see Dosage and Administration (2.1) and Clinical Studies (14.7)).

Levofloxacin is indicated in adult patients 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)).

Levofloxacin is indicated in adult patients 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.

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

Levofloxacin is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis in adults and pediatric patients, 6 months of age and older (see Dosage and Administration (2.2)). 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 Clinical Studies (14.9)).

Levofloxacin is indicated for treatment of plague, including pneumatic and septicemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older (see Dosage and Administration (2.2)).

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 Clinical Studies (14.10)).

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

Levofloxacin is indicated in adult patients 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)).

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

Levofloxacin is indicated in adult patients 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.

Levofloxacin is indicated in adult patients for the treatment of acute bacterial exacerbation of chronic bronchitis (ABECB) due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae,
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 in adult patients for the treatment of acute bacterial sinusitis (ABS) due to Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis [see Clinical Studies (14.4)].

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

1.15 Usage

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

Culture and susceptibility testing

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Dosage of Levofloxacin Tablets in Adult Patients with Creatinine Clearance ≥50 mL/minute

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 ≥ 50 mL/minute. For patients with creatinine clearance less than 50 mL/min, adjustments to the dosing regimen are required [see Dosage and Administration (2.3)].

Table 1: Dosage of Levofloxacin Tablets in Adult Patients with Creatinine Clearance greater than or equal to 50 mL/minute

<table>
<thead>
<tr>
<th>Type of Infection*</th>
<th>Dosed Every 24 hours</th>
<th>Duration (days)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial Pneumonia</td>
<td>750 mg</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Community Acquired Pneumonia‡</td>
<td>500 mg</td>
<td>7 to 14‡</td>
</tr>
<tr>
<td>Community Acquired Pneumonia§</td>
<td>750 mg§</td>
<td>5§</td>
</tr>
<tr>
<td>Complicated Skin and Skin Structure Infections (SSSI)</td>
<td>750 mg</td>
<td>7 to 14</td>
</tr>
<tr>
<td>Uncomplicated SSSI</td>
<td>500 mg</td>
<td>7 to 10</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>500 mg</td>
<td>28</td>
</tr>
<tr>
<td>Inhalational Anthrax (Post-Exposure), adult and pediatric patients weighing 50 kg or greater</td>
<td>500 mg see Table 2 below (2.2)</td>
<td>60*</td>
</tr>
<tr>
<td>Pediatric patients weighing 30 kg to less than 50 kg</td>
<td>10 to 14</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Plaque, adult and pediatric</td>
<td>500 mg see Table 2 below (2.2)</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Pediatric patients weighing 50 kg or greater</td>
<td>7 to 14</td>
<td></td>
</tr>
<tr>
<td>Pediatric patients weighing 30 kg to less than 50 kg</td>
<td>10 to 14</td>
<td>10 to 14</td>
</tr>
<tr>
<td>Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)¶</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)¶</td>
<td>250 mg¶</td>
<td>10¶</td>
</tr>
<tr>
<td>Uncomplicated Urinary Tract Infection</td>
<td>250 mg</td>
<td>3</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis (ABECB)</td>
<td>500 mg</td>
<td>7</td>
</tr>
<tr>
<td>Acute Bacterial Sinusitis (ABS)</td>
<td>750 mg</td>
<td>5</td>
</tr>
</tbody>
</table>

* Due to the designated pathogens [see Indications and Usage (1)].
† Sequential therapy (intravenous levofloxacin to oral levofloxacin tablets) may be instituted at the discretion of the healthcare provider.
‡ Due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae [see Indications and Usage (1.2)].
§ Due to Streptococcus pneumoniae (excluding multi-drug-resistant isolates [MDRSP]).
Antacids containing magnesium, aluminum, as well as sucralfate, metal cations such as Levofloxacin tablets should be administered at least two hours before or two hours after 2.4 Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Table 3 shows how to adjust dose based on creatinine clearance. In patients with renal impairment (creatinine clearance less than 50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced in these patients. In patients with renal impairment (creatinine clearance less than 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)]. No adjustment is necessary for patients with a creatinine clearance greater than or equal to 50 mL/minute. Table 3 shows how to adjust dose based on creatinine clearance. 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
Information on experienced peripheral neuropathy sensation including light touch, pain, temperature, position sense, and vibratory sensations. Irreversible in some patients and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Cases of sensory or sensorimotor axonal polyneuropathy have been reported with fluoroquinolones. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider for further advice. Patients of any age or without pre-existing risk factors have experienced these adverse reactions associated with fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Discontinue levofloxacin immediately 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. This adverse reaction most frequently involves the Achilles tendon and has also been reported with the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites. Tendinitis or tendon rupture can occur within hours or days of starting levofloxacin or as long as several months after completion of fluoroquinolone therapy. Tendinitis and tendon rupture can occur bilaterally. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is increased in patients over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Other factors that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Discontinue levofloxacin immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug. Avoid levofloxacin in patients who have a history of tendon disorders or tendon rupture.

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. 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.
5.4 Central Nervous System Effects

Psychiatric Adverse Reactions

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychoses, hallucinations, or paranoia; depression, or suicidal thoughts; anxiety, agitation, restlessness, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. Attempted or completed suicide have been reported, 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.

Central Nervous System Adverse Reactions

Fluoroquinolones, including levofloxacin, have been associated with an increased risk of seizures (convulsions), increased intracranial pressure (including pseudotumor cerebral), tremors, and lightheadedness. 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). If these reactions occur in patients receiving levofloxacin, discontinue levofloxacin and institute appropriate measures [see Adverse Reactions (6), Drug Interactions (7.4, 7.5), and Patient Counseling Information (17)].

5.5 Exacerbation of Myasthenia Gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Avoid levofloxacin tablets in patients with a known history of myasthenia gravis [see Adverse Reactions (6.3) and Patient Counseling Information (17)].

5.6 Other Serious and Sometimes Fatal Adverse Reactions

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

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

Discontinue levofloxacin immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and institute supportive measures [see Adverse Reactions (6) and Patient Counseling Information (17)].

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) and Patient Counseling Information (17)].

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) and Patient Counseling Information (17)].

5.9 Risk of Aortic Aneurysm and Dissection

Epidemiologic studies report an increased rate of aortic aneurysm and dissection within two months following use of fluoroquinolones, particularly in elderly patients. The cause for the increased risk has not been identified. In patients with a known aortic aneurysm or patients who are at greater risk for aortic aneurysms, reserve levofloxacin for use only when there are no alternative antibacterial treatments available.
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)]
- Risk of Aortic Aneurysm and Dissection [see Warnings and Precautions (5.9)]
• Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.10)]
• Prolongation of the QT Interval [see Warnings and Precautions (5.11)]
• Musculoskeletal Disorders in Pediatric Patients [see Warnings and Precautions (5.12)]
• Blood Glucose Disturbances [see Warnings and Precautions (5.13)]
• Photosensitivity/Phototoxicity [see Warnings and Precautions (5.14)]
• Development of Drug Resistant Bacteria [see Warnings and Precautions (5.15)]

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 (2.4)].

6.1 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 ≥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 (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
<th>% (N=7537)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>moniliasis</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia* [see Warnings and Precautions (5.4)]</td>
<td>4</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>headache</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>dizziness [see Warnings and Precautions (5.4)]</td>
<td>3</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>dyspnea [see Warnings and Precautions (5.7)]</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>diarrhea</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>constipation</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>abdominal pain</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>vomiting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>dyspepsia</td>
<td>2</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>rash [see Warnings and Precautions (5.7)]</td>
<td>2</td>
</tr>
<tr>
<td>Reproductive System and Breast Disorders</td>
<td>vaginitis</td>
<td>1†</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>edema</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>injection site reaction</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>chest pain</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4: Common (≥1%) Adverse Reactions Reported in Clinical Trials with levofloxacin

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>genital moniliasis</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>anemia</td>
</tr>
<tr>
<td></td>
<td>thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>granulocytopenia</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>allergic reaction [see Warnings and Precautions (5.6, 5.7)]</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>hyperkalemia</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>anxiety</td>
</tr>
<tr>
<td></td>
<td>agitation</td>
</tr>
</tbody>
</table>

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

### 6.2 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 estimate their frequency or establish a causal relationship to drug exposure.

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>pancytopenia, aplastic anemia, leukopenia, hemolytic anemia [see Warnings and Precautions (5.6)]</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>hypersensitivity reactions, sometimes fatal including: anaphylactic/anaphylactoid reactions, anaphylactic shock, angioneurotic edema, serum sickness [see Warnings and Precautions (5.6, 5.7)]</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>psychosis, paranoia, isolated reports of suicidal ideation, suicide attempt and completed suicide [see Warnings and Precautions (5.4)]</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>exacerbation of myasthenia gravis [see Warnings and Precautions (5.5)], anosmia, ageusia, parosmia, dysgeusia, peripheral neuropathy (may be irreversible) [see Warnings and Precautions (5.3)], isolated reports of encephalopathy</td>
</tr>
</tbody>
</table>
abnormal electroencephalogram (EEG)
dysphonia
pseudotumor cerebri [see Warnings and Precautions (5.4)]

Eye Disorders
uveits
vision disturbance, including diplopia
visual acuity reduced
vision blurred
scotoma

Ear and Labyrinth Disorders
hypoacusis
Tinnitus

Cardiac Disorders
isolated reports of torsade de pointes
electrocardiogram QT prolonged
[see Warnings and Precautions (5.11)]
tachycardia

Vascular Disorders
vasodilatation

Respiratory, Thoracic and Mediastinal Disorders
isolated reports of allergic pneumonitis [see Warnings and Precautions (5.6)]

Hepatobiliary Disorders
hepatic failure (including fatal cases)
hepatitis
jaundice
[see Warnings and Precautions (5.6), (5.8)]

Skin and Subcutaneous Tissue Disorders
bullous eruptions to include:
Stevens-Johnson Syndrome
toxic epidermal necrolysis
Acute Generalized Exanthematous Pustulosis (AGEP)
fixed drug eruptions
erythema multiforme
[see Warnings and Precautions (5.6)]
phototoxicity reaction [see Warnings and Precautions (5.14)]
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)]

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 multivitamin preparations with zinc or didanosine may substantially interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after oral levofloxacin administration.

7.2 Warfarin
No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, there have been reports during the postmarketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [see Adverse Reactions (6.3) and Patient Counseling Information (17)].

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 (5.13); Adverse Reactions (6.2) and Patient Counseling Information (17)].

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 t½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

7.7 Digoxin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin 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 t½ of levofloxacin were higher while CL/F and CL<sub>G</sub> 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

Risk Summary

Published information from case reports, case control studies and observational studies on levofloxacin administered during pregnancy have not identified any drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.

In animal reproduction studies, oral administration of levofloxacin to pregnant rats and rabbits during organogenesis at doses up to 9.4 times and 1.1 times the maximum recommended human dose (MRHD), respectively, did not result in teratogenicity. Fetal toxicity was seen in the rat study, but was absent at doses up to 1.2 times the maximum recommended human dose (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Levofloxacin was not teratogenic in an embryofetal development study in rats treated during organogenesis with oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the MRHD (based upon doses normalized for total body surface area). The oral dose of 50.0 mg/kg/day (high dose) to rats caused decreased fetal body weight and increased fetal mortality that was not seen at the next lower dose (mid-dose, 90 mg/kg/day, equivalent to 1.2 times the MRHD (based upon doses normalized for total body surface area). Maternal toxicity was limited to lower weight gain in the mid and high dose groups. No teratogenicity was observed in an embryofetal development study in rabbits dosed orally during organogenesis with doses as high as 50 mg/kg/day, which corresponds to 1.1 times the MRHD (based upon doses normalized for total body surface area). Maternal toxicity at that dose consisted of lower weight gain and decreased food consumption relative to controls and abortion in four of sixteen dams.

8.2 Lactation

Risk Summary

Published literature reports that levofloxacin is present in human milk following intravenous and oral administration (see Data). There is no information regarding effects of levofloxacin on milk production or the breastfed infant. Because of the potential risks of serious adverse reactions, in breastfed infants, for most indications, a lactating
Arthralgia was the most frequently occurring musculoskeletal disorder in both

8.4 Pediatric Use
Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. [see Warnings and Precautions (5.12) 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 pneumatic 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 of levofloxacin in pediatric patients below the age of six months have not been established.

Dosing in Pediatric Patients with Inhalational Anthrax or Plague
For the recommended levofloxacin tablet dosage in pediatric patients with inhalational anthrax or plague, see Dosage and Administration (2.2). Levofloxacin Tablets cannot be administered to pediatric patients who weigh less than 30 kg because of the limitations of the available strengths. Alternative formulations of levofloxacin may be considered for pediatric patients who weigh less than 30 kg.

Adverse Reactions
In clinical trials, 1534 pediatric patients (6 months to 16 years of age) were treated with oral and intravenous levofloxacin. Pediatric patients 6 months to 5 years of age received levofloxacin 10 mg/kg twice a day and pediatric patients greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days. Levofloxacin Tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths [see Dosage and Administration (2.2)].

A subset of pediatric patients 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. Pediatric patients treated with levofloxacin had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 7. Levofloxacin Tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths [see Dosage and Administration (2.2)].

Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

<table>
<thead>
<tr>
<th>Follow-up Period</th>
<th>Levofloxacin N = 1340</th>
<th>Non-Fluoroquinolone N = 893</th>
<th>p-value1</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 days</td>
<td>28 (2.1%)</td>
<td>8 (0.9%)</td>
<td>p = 0.038</td>
</tr>
<tr>
<td>1 year‡</td>
<td>46 (3.4%)</td>
<td>16 (1.8%)</td>
<td>p = 0.025</td>
</tr>
</tbody>
</table>

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

1.8
2-sided Fisher’s Exact Test

There were 1199 levofloxacin-treated and 804 non-fluoroquinolone-treated pediatric patients 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 pediatric patients enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both
treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) levofloxacin-treated pediatric patients and most were treated with analgesics. The median time to resolution was 7 days for levofloxacin-treated pediatric patients and 9 for non-fluoroquinolone-treated children (approximately 80% resolved within 2 months in both groups). No pediatric patient had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.

Vomiting and diarrhea were the most frequently reported adverse reactions, occurring in similar frequency in the levofloxacin-treated and non-fluoroquinolone-treated pediatric patients.

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

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as levofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing levofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [see Boxed Warning; Warnings and Precautions (5.2); and Adverse Reactions (6.3)].

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

Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see Warnings and Precautions (5.8)].

Epidemiologic studies report an increased rate of aortic aneurysm and dissection within two months following use of fluoroquinolones, particularly in elderly patients [see Warnings and Precautions (5.9)].

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 (5.11)].

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 renal impairment (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 patients with hepatic impairment 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 (approximately 10 or 19 times MRHD in mice and rats, respectively) and 250 mg/kg IV produced significant mortality (estimated to be greater than or equal to 50%) in rodents.

11 DESCRIPTION

Levofloxacin tablets, USP is a synthetic antibacterial agent for oral administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (−)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (−)-(S)-9-
fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate.

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

![Chemical Structure of Levofloxacin](image-url)

The empirical formula is C_{18}H_{21}FN_3O_4·\(\frac{1}{2}\)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+}.

Levofloxacin tablets, USP 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 ± SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following administration of the oral tablets, are summarized in Table 8.

**Table 8: Mean ± SD Levofloxacin PK Parameters**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>(C_{max}) (mcg/mL)</th>
<th>(T_{max}) (h)</th>
<th>AUC (mcg·h/mL)</th>
<th>CL/F1 (mL/min)</th>
<th>Vd/F2 (L)</th>
<th>(t_{1/2}) (h)</th>
<th>CLR (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg oral tablet(^3)</td>
<td>2.8 ± 0.4</td>
<td>1.6 ± 1.0</td>
<td>27.2 ± 3.9</td>
<td>156 ± 20</td>
<td>ND</td>
<td>7.3 ± 0.9</td>
<td>142 ± 21</td>
</tr>
<tr>
<td>500 mg oral tablet(^3)</td>
<td>5.1 ± 0.8</td>
<td>1.3 ± 0.6</td>
<td>47.9 ± 6.8</td>
<td>178 ± 28</td>
<td>ND</td>
<td>6.3 ± 0.6</td>
<td>103 ± 30</td>
</tr>
<tr>
<td>750 mg oral tablet(^3)</td>
<td>9.3 ± 1.6</td>
<td>1.6 ± 0.8</td>
<td>101 ± 20</td>
<td>129 ± 24</td>
<td>83 ± 17</td>
<td>7.5 ± 0.9</td>
<td>ND</td>
</tr>
<tr>
<td>Multiple dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500 mg every 24h oral tablet(^3)</td>
<td>5.7 ± 1.4</td>
<td>1.1 ± 0.4</td>
<td>47.5 ± 6.7</td>
<td>175 ± 25</td>
<td>102 ± 22</td>
<td>7.6 ± 1.6</td>
<td>116 ± 31</td>
</tr>
<tr>
<td>750 mg every 24h oral tablet(^4)</td>
<td>8.6 ± 1.9</td>
<td>1.4 ± 0.5</td>
<td>90.7 ± 17.6</td>
<td>143 ± 29</td>
<td>100 ± 16</td>
<td>8.8 ± 1.5</td>
<td>116 ± 28</td>
</tr>
<tr>
<td>500 mg oral tablet single dose, effects of gender and age:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male(^5)</td>
<td>5.5 ± 1.1</td>
<td>1.2 ± 0.4</td>
<td>54.4 ± 18.9</td>
<td>166 ± 44</td>
<td>89 ± 13</td>
<td>7.5 ± 2.1</td>
<td>126 ± 38</td>
</tr>
<tr>
<td>Female(^6)</td>
<td>7.0 ± 1.6</td>
<td>1.7 ± 0.5</td>
<td>67.7 ± 24.2</td>
<td>136 ± 44</td>
<td>62 ± 16</td>
<td>6.1 ± 0.8</td>
<td>106 ± 40</td>
</tr>
<tr>
<td>Young(^7)</td>
<td>5.5 ± 1.0</td>
<td>1.6 ± 0.6</td>
<td>47.5 ± 9.8</td>
<td>182 ± 35</td>
<td>83 ± 18</td>
<td>6.0 ± 0.9</td>
<td>140 ± 33</td>
</tr>
<tr>
<td>Elderly(^8)</td>
<td>7.0 ± 1.6</td>
<td>1.4 ± 0.5</td>
<td>74.7 ± 23.3</td>
<td>121 ± 33</td>
<td>67 ± 19</td>
<td>7.6 ± 2.0</td>
<td>91 ± 29</td>
</tr>
<tr>
<td>500 mg oral single dose tablet, patients with renal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLCR 50–80 mL/min</td>
<td>7.5 ± 1.8</td>
<td>1.5 ± 0.5</td>
<td>95.6 ± 11.8</td>
<td>88 ± 10</td>
<td>ND</td>
<td>9.1 ± 0.9</td>
<td>57 ± 8</td>
</tr>
</tbody>
</table>
No levofloxacin crystals were found in any of the urine samples freshly collected from respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. Glomerular filtration. Concomitant administration of either cimetidine or probenecid filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its apparent total body clearance and renal clearance range from approximately 144 to 226 L/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 renal clearance, respectively, indicating the drug is renally eliminated.

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 renal clearance, respectively. No levofloxacin crystals were found in any of the urine samples freshly collected from.
some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones. Resistance to levofloxacin due to spontaneous mutation or through altered efflux.

Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. 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.

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.

Resistance

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

Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10⁻⁹ to 10⁻¹²). Cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones.
may be susceptible to levofloxacin.

**Antimicrobial Activity**

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):

**Aerobic bacteria**

**Gram-Positive Bacteria**

*Enterococcus faecalis*

*Staphylococcus aureus* (methicillin-susceptible isolates)

*Staphylococcus epidermidis* (methicillin-susceptible isolates)

*Staphylococcus saprophyticus*

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

*Streptococcus pyogenes*

**Gram-Negative Bacteria**

*Enterobacter cloacae*

*Escherichia coli*

*Haemophilus influenzae*

*Haemophilus parainfluenzae*

*Klebsiella pneumoniae*

*Legionella pneumophila*

*Moraxella catarrhalis*

*Proteus mirabilis*

*Pseudomonas aeruginosa*

*Serratia marcescens*

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

**Other microorganisms**

*Chlamydophila pneumoniae*

*Mycoplasma pneumoniae*

The following in *vivo* data are available, but their clinical significance is unknown. At least 90 percent of the following bacteria exhibit an *in vitro* minimum inhibitory concentrations (MIC) less than or equal to the susceptible breakpoint for levofloxacin against isolates of similar genus or organism group. However, efficacy of levofloxacin in treating clinical infections caused by these bacteria has not been established in adequate and well-controlled clinical trials.

**Aerobic bacteria**

**Gram-Positive Bacteria**

*Staphylococcus haemolyticus*

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

*β-hemolytic Streptococcus (Group G)*

*Streptococcus agalactiae*

*Streptococcus milleri*

*Viridans group streptococci*

*Bacillus anthracis*

**Gram-Negative Bacteria**

*Acinetobacter baumannii*

*Acinetobacter lwoffii*

*Bordetella pertussis*

*Citrobacter koseri*

*Citrobacter freundii*

*Enterobacter aerogenes*

*Enterobacter sakazakii*

*Klebsiella oxytoca*

*Morganella morganii*

*Pantoea agglomerans*

*Proteus vulgaris*

*Providencia rettgeri*

*Providencia stuartii*

*Pseudomonas fluorescens*
Yersinia pestis
Anaerobic bacteria
Gram-Positive Bacteria
Clostridium perfringens

Susceptibility Tests
For specific information regarding susceptibility test interpretive criteria and associated test methods and quality control standards recognized by FDA for this drug, please see: https://www.fda.gov/STIC.

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 Maximum Recommended Human Dose (MRHD) (750 mg) after normalization for total 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 Cmax.

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 MRHD and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the MRHD after normalization for total 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 (5.12)). 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 arthrototoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine (dosing was terminated in the low and mid-dose groups on Day 9 due to similar findings at the mid-dose). 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. The low and mid-dose groups in that study were also evaluated by electron microscopy, revealing compound-related ultrastructural effects in articular cartilage chondrocytes at the end of treatment and at the end of recovery in both of those doses.

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 posttherapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and microbiological eradication rates by pathogen are detailed in Table 9.

### Table 9: Clinical Success Rates and Bacteriological Eradication Rates (Nosocomial Pneumonia)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>N</th>
<th>Levofloxacin No. (% of Patients Microbiologic/Clinical Outcomes)</th>
<th>Imipenem/Cilastatin No. (% of Patients Microbiologic/Clinical Outcomes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSSA*</td>
<td>21</td>
<td>14 (66.7)/13 (61.9)</td>
<td>19 (68.4)/15 (78.9)</td>
</tr>
<tr>
<td>*P. aeruginosa†</td>
<td>17</td>
<td>10 (58.8)/11 (64.7)</td>
<td>17 (59.4)/7 (41.2)</td>
</tr>
<tr>
<td>S. marcescens</td>
<td>11</td>
<td>9 (81.8)/7 (63.6)</td>
<td>7 (28.6)/3 (42.9)</td>
</tr>
<tr>
<td>E. coli</td>
<td>12</td>
<td>10 (83.3)/7 (58.3)</td>
<td>11 (73.6)/8 (72.7)</td>
</tr>
<tr>
<td>K. pneumonia‡</td>
<td>11</td>
<td>9 (81.8)/5 (45.5)</td>
<td>7 (65.7)/3 (42.9)</td>
</tr>
<tr>
<td>H. influenza</td>
<td>16</td>
<td>13 (81.3)/10 (62.5)</td>
<td>15 (93.3)/11 (73.3)</td>
</tr>
<tr>
<td>S. pneumonia</td>
<td>4</td>
<td>3 (75.0)/3 (75.0)</td>
<td>7 (71.4)/4 (57.1)</td>
</tr>
</tbody>
</table>

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

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

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, 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 10.

### Table 10: Bacteriological Eradication Rates Across 2 Community Acquired Pneumonia Clinical Studies

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

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

Levofloxacin was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant Streptococcus pneumoniae (MDRSP). MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 11.

### Table 11: Clinical and Bacterial Success Rates for Levofloxacin Treated
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.

<table>
<thead>
<tr>
<th>Screening Susceptibility</th>
<th>Clinical Success</th>
<th>Bacteriological Success*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>%</td>
</tr>
<tr>
<td>Penicillin-resistant</td>
<td>16/17</td>
<td>94.1</td>
</tr>
<tr>
<td>2nd generation Cephalosporin resistant</td>
<td>31/32</td>
<td>96.9</td>
</tr>
<tr>
<td>Macrolide-resistant</td>
<td>28/29</td>
<td>96.6</td>
</tr>
<tr>
<td>Tetracycline-resistant</td>
<td>12/12</td>
<td>100</td>
</tr>
</tbody>
</table>

* 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.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 12.

Table 12: Clinical Success and Bacteriologic Eradication Rates for Resistant Streptococcus pneumoniae (Community Acquired Pneumonia)

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

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 13.

Table 13: Bacteriological Eradication Rates (Community-Acquired Pneumonia)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bacteriological Eradication</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumoniae</td>
<td>19/20 (95%)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>12/12 (100%)</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
<td>10/10 (100%)</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>26/27 (96%)</td>
</tr>
<tr>
<td>Chlamydia pneumoniae</td>
<td>13/15 (87%)</td>
</tr>
</tbody>
</table>

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, IV or orally, every day for five days or levofloxacin 500 mg IV or orally, every day 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
### 14.5 Complicated Skin and Skin Structure Infections

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

Among those who could be evaluated clinically 2-5 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 15.

### 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 16.

---

**Table 14:** Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin 750 mg x 5 days</th>
<th>Levofloxacin 500 mg x 10 days</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Streptococcus pneumoniae</strong></td>
<td>25/27 (92.6%)</td>
<td>26/27 (96.3%)</td>
</tr>
<tr>
<td><strong>Haemophilus influenzae</strong></td>
<td>19/21 (90.5%)</td>
<td>25/27 (92.6%)</td>
</tr>
<tr>
<td><strong>Moraxella catarrhals</strong></td>
<td>10/11 (90.9%)</td>
<td>13/13 (100%)</td>
</tr>
</tbody>
</table>

*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.*

---

**Table 15:** Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin (N=136)</th>
<th>Ciprofloxacin (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td>15</td>
<td>14 (93.3%)</td>
</tr>
<tr>
<td><strong>E. faecalis</strong></td>
<td>54</td>
<td>39 (72.2%)</td>
</tr>
<tr>
<td><strong>S. epidermidis</strong></td>
<td>11</td>
<td>9 (81.8%)</td>
</tr>
</tbody>
</table>

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

---

**Table 16:** Bacteriological Eradication at Test-of-Cure

<table>
<thead>
<tr>
<th>Levofloxacin 750 mg orally or IV once daily for 5 days</th>
<th>Ciprofloxacin 400 mg IV/500 mg orally twice daily for 10 days</th>
<th>Overall Difference [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N Group (cUTI or AP)</td>
<td>n/N Group</td>
<td>Levofloxacin-Ciprofloxacin</td>
</tr>
<tr>
<td>Overall mITT Population</td>
<td></td>
<td></td>
</tr>
<tr>
<td>252/333</td>
<td>239/318</td>
<td>75.2</td>
</tr>
</tbody>
</table>

*Note: The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in Table 14.*
1.12 The predicted steady-state pharmacokinetic parameters in the corresponding total plasma exposure (AUC oral or intravenous once daily is $5.7 \pm 1.4$ and $6.4 \pm 0.8 \text{ mcg/mL, respectively}$; and mean (± SD) steady state peak plasma concentration in human adults receiving $500 \text{ mg}$ Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The [seerecommended oral and intravenous dosage regimens of inhalational anthrax are reached or exceeded in adult and pediatric patients receiving statistically significant improvement in survival over placebo in the rhesus monkey model of inhalation anthrax. The mean plasma concentrations of levofloxacin associated with a [achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. The effectiveness of levofloxacin for this indication is based on plasma concentrations presented in Table 17.

### Table 17: Bacteriological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to Levofloxacin 750 mg QD for 5 Days Treatment

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bacteriological Eradication Rate (n/N)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>155/172</td>
<td>90</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>20/23</td>
<td>87</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>12/12</td>
<td>100</td>
</tr>
</tbody>
</table>

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

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

To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of levofloxacin, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing levofloxacin 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 36% 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 18.

### Table 18: Bacteriological Eradication Overall (cUTI or AP) at Test-Of-Cure*

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Levofoxacin 250 mg once daily for 10 days n/N</th>
<th>%</th>
<th>Ciprofloxacin 500 mg twice daily for 10 days n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Population†</td>
<td>174/209</td>
<td>83.3</td>
<td>184/219</td>
<td>84.0</td>
</tr>
<tr>
<td>Microbiologically Evaluable Population‡</td>
<td>164/177</td>
<td>92.7</td>
<td>159/171</td>
<td>93.0</td>
</tr>
</tbody>
</table>

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

### 14.9 Inhalational Anthrax (Post-Exposure)

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

Levofoxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is $5.7 \pm 1.4$ and $6.4 \pm 0.8 \text{ mcg/mL, respectively}$; and the corresponding total plasma exposure (AUC$_{0-24}$) is $47.5 \pm 6.7$ and $54.6 \pm 11.1 \text{ mcg.h/mL, respectively}$. 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)]. Levofloxacin tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths [see Dosage and Administration (2.2)].

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 abnormalities) 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 (5.12) and Use in Specific Populations (8.4)].

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD50 (~2.7 x 10^6) spores (range 17 – 118 LD50) of B. anthracis (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_max (1 hour post-dose) following oral dosing to steady state ranged from 2.79 to 4.87 mcg/mL. Steady state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL. Mean (SD) steady state AUC_0-24 was 33.4 ± 3.2 mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10) [P= 0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

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

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

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_0-24) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_0-24) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)]. Levofloxacin tablets can only be administered to pediatric patients with inhalational anthrax (post-exposure) or plague who are 30 kg or greater due to the limitations of the available strengths [see Dosage and Administration (2.2)].

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD50 (range 3 to 145 LD50) of Yersinia pestis (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the Y. pestis strain used in this study was 0.03 mcg/mL. Mean plasma concentrations of levofloxacin achieved at the end of a single 30-min infusion ranged from 2.84 to 3.50 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from <0.03 to 0.06 mcg/mL. Mean (SD) AUC_0-24 was 11.9 (3.1) mcg.h/mL (range 9.50 to 16.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. levofloxacin or placebo beginning 6 hrs of the onset of telemetered fever (≥ 39°C for more than 1 hour). Mortality in the levofloxacin group was significantly lower (1/17) compared to the placebo group (7/7) [p<0.001, Fisher's Exact Test; exact 95% confidence interval (-99.9%, -55.5%) for the difference in mortality]. One levofloxacin-treated animal was euthanized on Day 4 due to a gastric complication; it had a blood culture positive for Y. pestis on Day 3 and all subsequent daily blood cultures from Day 4 through Day 7 were negative.

16 HOW SUPPLIED/STORAGE AND HANDLING
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.
- 500 mg tablets are Yellow, oval, biconvex, film coated tablets, debossed '500' on one side and 'C289' on the other side.
- 750 mg tablets are White, oval, biconvex, film coated tablets, debossed '750' on one side and 'C287' on the other side.

Dispense in a well-closed container as defined in the USP. Use child-resistant closure (as
17 PATIENT COUNSELING INFORMATION

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

Serious Adverse Reactions

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

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

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

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

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

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

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

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

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

- **Aortic aneurysm and dissection:** Inform patients to seek emergency medical care if they experience sudden chest, stomach, or back pain.

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

- **Prolongation of the QT Interval:** Instruct patients to inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Instruct patients to notify their physician if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

- **Musculoskeletal Disorders in Pediatric Patients:** Instruct parents to inform their child's physician if the child has a history of joint-related problems before taking this drug. Inform parents of pediatric patients to notify their child's physician of any joint-related problems that occur during or following levofloxacin therapy (see Warnings and Precautions (5.12) and Use in Specific Populations (8.4)).

- **Photosensitivity/Phototoxicity:** Inform patients that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolones. Inform patients to minimize or avoid exposure to natural or artificial sunlight (including sunlamp beds or UVA/UVB 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.

- **Lactation:** Advise a lactating woman that she may pump and discard during treatment with levofloxacin and for an additional 2 days after the last dose. Alternatively, advise a lactating woman that breastfeeding is not recommended during treatment with levofloxacin and for an additional 2 days after the last dose (see Use in Specific Populations (8.2)).

Required. Store at 20ºC to 25ºC (68ºF to 77ºF) [See USP Controlled Room Temperature]
Antibacterial Resistance

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

Administration with Food, Fluids, and Concomitant Medications

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

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

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

Drug Interactions with Insulin, Oral Hypoglycemic Agents, and Warfarin

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

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

Plague and Anthrax Studies

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

Manufactured by:
Cipla Ltd.
Verna Goa, India.

Manufactured for:
Cipla USA, Inc.
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MEDICATION GUIDE

LEVOFLOXACIN TABLETS, USP

[LEE-voe-FLOX-a-sin]

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 swelling of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendon 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 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: 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. 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 people 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
  - The tendon problems may be permanent.

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

The nerve damage may be permanent.

3. Central Nervous System (CNS) effects. Mental health problems and seizures have been reported in people who take fluoroquinolone antibacterial medicines, including levofloxacin. Tell your healthcare provider if you have a history of mental health problems, including depression, or 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, nightmares
  - or sense things that are
  - feel light-headed or dizzy
  - not there (hallucinations)
  - feel more suspicious (paranoia)
  - feel restless or agitated
  - suical thoughts or acts
  - tremors
  - headaches that will not go away, with or without blured vision
  - confusion
  - memory problems
  - depression
  - reduced awareness of surroundings
  - false or strange thoughts or beliefs (delusions)

The CNS changes may be permanent.

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 of any muscle weakness or breathing problems.

What are levofloxacin tablets?

Levofloxacin tablets are 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
  - skin infections, complicated and uncomplicated
  - chronic prostate infection
  - inhalation anthrax germs
  - plague
  - urinary tract infections, complicated and uncomplicated
  - acute kidney infection (pyelonephritis)
  - acute sinus infection
  - acute worsening of chronic bronchitis

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 people with uncomplicated urinary tract infections, acute bacterial exacerbation of chronic bronchitis, or acute bacterial sinusitis if there are other treatment options available.

Levofloxacin tablets are also used to treat children who weigh at least 66 pounds (or at least 30 kilograms) and may have breathed in anthrax germs, have plague, or been exposed to plague germs.

It is not known if levofloxacin tablets are 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.

Before you take levofloxacin tablets, tell your healthcare provider about all of your medical conditions, including if you:

- have tendon problems; levofloxacin tablets should not be used in people who have a history of tendon problems.
- have a problem that causes muscle weakness (myasthenia gravis); Levofloxacin tablets should not be used in people who have a known history of myasthenia gravis.
- have a history of mental health problems, including depression.
- have central nervous system problems such as seizures (epilepsy).
- have nerve problems; levofloxacin tablets should not be used in people 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. Levofloxacin passes into your breast milk. You should not breastfeed during treatment with levofloxacin and for 2 days after taking your last dose of levofloxacin. You may pump your breast milk and throw it away during treatment with levofloxacin and for 2 days after taking your last dose of levofloxacin. If you are taking levofloxacin for inhalational anthrax, you and your healthcare provider should decide whether you can continue breastfeeding while taking levofloxacin.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter 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 your healthcare provider tells you to take it.
- Take levofloxacin tablets at the same time each day.
- Drink plenty of fluids while you take levofloxacin tablets.
- Levofloxacin tablets can be taken with or without food.
- If you miss a dose of levofloxacin tablets and it is:
  - 8 hours or more until your next scheduled dose, take your missed dose right away. Then take the next dose at your regular time.
  - less than 8 hours until your next scheduled dose, do not take the missed dose. Take the next dose at your regular time.
- 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 nerve problem. See "What is the most important information I should know about levofloxacin tablets?".
  - you have a central nervous system problem. 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 affect 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 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 may 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 have any of the following symptoms of a severe allergic reaction:
  - hives
  - trouble breathing or swallowing
  - swelling of the lips, tongue, face
  - throat tightness, hoarseness
  - rapid heartbeat
  - faint
  - skin rash
- Skin rash may happen in people taking levofloxacin tablets, even after only 1 dose. Stop taking levofloxacin tablets at the first sign of a skin rash and immediately 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
  - pain or tenderness in the upper right side of your stomach-area
  - 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).
- Aortic aneurysm and dissection. Tell your healthcare provider if you have ever been told that you have an aortic aneurysm, a swelling of the large artery that carries blood from the heart to the body. Get emergency medical help right away if you have sudden chest, stomach, or back pain.
- Intestine infection (Clostridium difficile-associated diarrhea). Clostridium difficile-associated diarrhea (CDAD) can happen with many 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. CDAD 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:
  - nausea
  - headache
  - diarrhea
  - insomnia
  - constipation
  - 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.

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 20ºC to 25ºC (68ºF to 77ºF) [See USP Controlled Room Temperature].
- Keep levofloxacin tablets in a tightly closed container.

**General information about the safe and effective use of levofloxacin tablets**

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 health professionals.

**What are the ingredients in levofloxacin tablets?**

250 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 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
10 Independence Boulevard, Suite 300
Warren, NJ - 07059

**Disclaimer:** Other brands listed are the registered trademarks of their respective owners and are not trademarks of Cipla Limited.

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

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: 07/2020

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

Rx ONLY

NDC 69097-282-70

Levofloxacin
Tablets, USP
Rx ONLY
NDC 69097-282-07
Levofloxacin
Tablets, USP
250 mg
Once-A-Day
PHARMACIST:
Please dispense with Medication Guide
50 Tablets (Brownish Pink)
Cipla

Rx ONLY
NDC 69097-289-70
Levofloxacin
Tablets, USP
500 mg
Once-A-Day
PHARMACIST:
Please dispense with Medication Guide
50 Tablets (Yellow)
Cipla
Rx ONLY
NDC 69097-289-07
Levofloxacin
Tablets, USP
500 mg
Once-A-Day
PHARMACIST:
Please dispense with Medication Guide
100 Tablets (Yellow)
Cipla

Rx ONLY
NDC 69097-287-81
Levofloxacin
Tablets, USP
750 mg
Once-A-Day
PHARMACIST:
Please dispense with Medication Guide
20 Tablets (White)
Cipla
**LEVOFLOXACIN**
levofloxacin tablet

### Product Information

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<tr>
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<td>CROSCARMELLOSE SODIUM</td>
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<td>Povidone</td>
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<td>Hypromelloses</td>
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<td>TITANIUM DIOXIDE</td>
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<tr>
<td>POLYETHYLENE GLYCOL, UNSPECIFIED</td>
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### Product Characteristics

- **Color**: BROWN (Brownish-pink)
- **Score**: no score
- **Shape**: OVAL (Biconvex)
- **Size**: 13mm
- **Flavor**: Imprint Code 250;C282
- **Contains**:

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**Rx ONLY**
NDC 69097-287-07
Levofloxacin Tablets, USP
750 mg
Once-A-Day
PHARMACIST:
Please dispense with Medication Guide
100 Tablets (White)
Cipla
**Product Information**

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**Active Ingredient/Active Moiety**

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**Inactive Ingredients**

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<tr>
<td>MAGNESIUM STEARATE (UNII: 70979M6I30)</td>
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<td>CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)</td>
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**LEVOFLOXACIN**

levofloxacin tablet

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### Labeler
- Cipla USA Inc. (078719707)

### Registrant
- Cipla USA Inc. (078719707)

### Establishment

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Revised: 12/2022  Cipla USA Inc.