LEVOFLOXACIN - levofloxacin tablet

FDA-approved Medication Guide

Levofloxacin is a fluoroquinolone antibacterial indicated in adults (≥18 years of age) with infections caused by designated, susceptible bacteria. See full prescribing information for LEVOFLOXACIN tablets, USP.

DOSAGE FORMS AND STRENGTHS

- Tablets
  - 250 mg
  - 500 mg
  - 750 mg

DOSAGE AND ADMINISTRATION

- For oral use.
- Do not confuse levofloxacin with levamisole.
- Tablets should be swallowed whole.
- Oral dosage should be adjusted based on the age, weight, sex, and renal function of the patient and the sensitivity of the infecting organisms.
- Do not use in patients with known or suspected hypersensitivity to levofloxacin or other quinolones.
- Do not use in patients with known prolongation of the QT interval.
- Do not use in patients with congenital or acquired QT interval prolongation.
- Do not use in patients with severe or moderate hepatic impairment.
- Do not use in patients with severe or moderate renal impairment.
- Do not use in patients with history of tendon rupture.
- Do not use in patients with known prolongation of the QT interval.
- Do not use in patients with congenital or acquired QT interval prolongation.
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- Do not use in patients with congenital or acquired QT interval prolongation.
- Do not use in patients with severe or moderate hepatic impairment.
- Do not use in patients with severe or moderate renal impairment.
- Do not use in patients with history of tendon rupture.
1.1 Nosocomial Pneumonia

the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

performed periodically during therapy will provide information about the continued susceptibility of

fairly rapidly during treatment with levofloxacin tablets, USP. Culture and susceptibility testing

As with other drugs in this class, some isolates of

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

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and

prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When

To reduce the development of drug-resistant bacteria and maintain the effectiveness of levofloxacin

WARNING:

Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis and tendon ruptures in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (See Warnings and Precautions (5.2)).

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

WARNING:

To reduce the development of drug-resistant bacteria and maintain the effectiveness of levofloxacin tablets, USP and other antibacterial drugs, levofloxacin tablets, USP should be used only in the treatment or prevention of 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.

Levofloxacin Tablets, USP is indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed in this section.

Culture and susceptibility testing

Appropriate culture and susceptibility tests should be performed before therapy is initiated and should be performed periodically during therapy to determine their susceptibility to levofloxacin tablets, USP. Therapy with levofloxacin tablets, USP 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 tablets, USP. Culture and susceptibility testing performed periodically during therapy should provide information about the continued susceptibility of the pathogen to the anti-pseudomonal agent and also the possible emergence of bacterial resistance.

1.1 Nosocomial Pneumonia

Levofloxacin tablets, USP is indicated for the treatment of nosocomial pneumonia due to methicillin-susceptible Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli,
Klebsiella pneumoniae, Haemophilus influenzae or Streptococcus pneumoniae. Adjunctive therapy should be used as clinically indicated. Where Pseudomonas aeruginosa is a documented or presumptive pathogen, a combination therapy with an aminoglycoside (e.g., amikacin) is recommended (see Clinical Studies (14.14)).

1.2 Community-Acquired Pneumonia—7 to 14-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of community-acquired pneumonia due to methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug-resistant Streptococcus pneumoniae [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae (see Dosage and Administration (2.1) and Clinical Studies (14.2)).

MDRSP isolates are resistant to two or more of the following antimicrobials: penicillin (MIC ≥2 mcg/mL), chloramphenicol, trimethoprim, and sulfamethoxazole/trimethoprim.

1.3 Community-Acquired Pneumonia—5-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis (see Clinical Studies (14.14)).

1.4 Acute Bacterial Sinusitis—5-Day and 10-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of acute bacterial sinusitis due to Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis (see Clinical Studies (14.4)).

1.5 Acute Bacterial Exacerbation of Chronic Bronchitis
Levofloxacin tablets, USP is indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis.

1.6 Complicated Skin and Skin Structure Infections
Levofloxacin tablets, USP is indicated for the treatment of complicated skin and skin structure infections due to methicillin-sensitive Staphylococcus aureus, Streptococcus pyogenes, or Pseudomonas aeruginosa (see Clinical Studies (14.3)).

1.7 Uncomplicated Skin and Skin Structure Infections
Levofloxacin tablets, USP is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pustulosis, wound infections, due to methicillin-sensitive Staphylococcus aureus, or Streptococcus pyogenes.

1.8 Chronic Bacterial Prostatitis
Levofloxacin tablets, USP is indicated for chronic bacterial prostatitis due to Escherichia coli, Enterococcus faecalis, or methicillin-sensitive Staphylococcus epidermidis (see Clinical Studies (14.3)).

1.9 Complicated Urinary Tract Infections—5-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of complicated urinary tract infection due to Escherichia coli, Klebsiella pneumoniae, or Pseudomonas aeruginosa (see Clinical Studies (14.7)).

1.10 Complicated Urinary Tract Infections—10-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of complicated urinary tract infection (mild to moderate) due to Enterococcus faecalis, Enterococcus faecium, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa or Pseudomonas aeruginosa (see Clinical Studies (14.4)).

1.11 Acute Pyelonephritis—5 to 10-Day Treatment Regimen
Levofloxacin tablets, USP is indicated for the treatment of acute pyelonephritis caused by Escherichia coli, including cases with concurrent bacteremia (see Clinical Studies (14.7, 14.8)).

1.12 Uncomplicated Urinary Tract Infections
Levofloxacin tablets, USP is indicated for the treatment of uncomplicated urinary tract infections (mild to moderate) due to Escherichia coli, Klebsiella pneumoniae, or Staphylococcus saprophyticus.

1.13 Inhalational Anthrax (Post-Exposure)
Levofloxacin tablets, USP is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis. The effectiveness of levofloxacin tablets, USP is based on plasma concentration 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 tablets for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk (see Dosage and Administration (2.1, 2.2), and Clinical Studies (14.5)).

1.14 Plague
Levofloxacin tablets, USP is indicated for treatment of plague, including pneumonic and septicaemic plague, due to Yersinia pestis. To treat pneumonic plague and septicaemic plague in adults and pediatric patients, 6 months of age and older. Efficacy studies of levofloxacin tablets could not be conducted in humans with plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals (see Dosage and Administration (2.1, 2.2) and Clinical Studies (14.6)).

2 DOSAGE AND ADMINISTRATION

2.1 Dosage in Adult Patients with Normal Renal Function

The usual dosage of levofloxacin tablets, USP 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/min. For patients with creatinine clearance < 50 mL/min, adjustments to the dosage regimen are required (see Dosage and Administration (2.3))

<table>
<thead>
<tr>
<th>Type of Infection*</th>
<th>Dosed Every 24 Hours</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonscrotal Pneumonia</td>
<td>750 mg</td>
<td>7–14</td>
</tr>
<tr>
<td>Community Acquired Pneumonia</td>
<td>750 mg</td>
<td>7–14</td>
</tr>
<tr>
<td>Community Acquired Pneumonia</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Acute Bacterial Sepsis</td>
<td>500 mg</td>
<td>10–14</td>
</tr>
<tr>
<td>Acute Bacterial Exacerbation of Chronic Bronchitis</td>
<td>500 mg</td>
<td>7</td>
</tr>
<tr>
<td>Complicated Skin and Skin Structure Infections (ISSS)</td>
<td>750 mg</td>
<td>7–14</td>
</tr>
<tr>
<td>Uncomplicated ISSS</td>
<td>500 mg</td>
<td>7–10</td>
</tr>
<tr>
<td>Chronic Bacterial Prostatitis</td>
<td>500 mg</td>
<td>7–14</td>
</tr>
<tr>
<td>Complicated Urinary Tract Infections (cUTI) or Acute Pyelonephritis (AP)*</td>
<td>750 mg</td>
<td>5</td>
</tr>
<tr>
<td>Complicated Urinary Tract Infections (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>Inhalational Anthrax (Post-Exposure)</td>
<td>500 mg</td>
<td>60 *</td>
</tr>
<tr>
<td>adult and pediatric patients</td>
<td>500 mg</td>
<td>60 *</td>
</tr>
<tr>
<td>Pediatric patients &lt; 50 kg and ≥ 6 months of age</td>
<td>500 mg</td>
<td>60 *</td>
</tr>
<tr>
<td>Pediatric patients with creatinine clearance between 50 and 60 mL/min</td>
<td>500 mg</td>
<td>60 *</td>
</tr>
<tr>
<td>Pediatric patients with creatinine clearance between 30 and 50 mL/min</td>
<td>500 mg</td>
<td>10 to 14</td>
</tr>
</tbody>
</table>

*See Table 2 below (2.2).

**For the designated pathogens (see Indications and Usage (1.1))

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

(1) Due to methicillin-sensitive 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))

(2) Due to Streptococcus pneumoniae (including multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, or Mycoplasma pneumoniae (see Indications and Usage (1.2))

(3) This regimen is indicated for (1) or (2) due to Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa and AP due to P. aeruginosa.

(4) Prolonged administration should begin as soon as possible after suspected or confirmed exposure to aerosolized B. anthracis. This indication is based on a surrogate endpoint. Levofloxacin plasma concentration achieved in humans is reasonably likely to predict clinical benefit (see Clinical Studies (14.6)).

(5) The safety of levofloxacin tablets for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of maculopapular adverse events compared to controls has been observed in pediatric patients (see Warnings and Precautions (5.10)). Use in specific Populations (5.6) and Clinical Studies (14.6). Prolonged levofloxacin therapy should only be used when the benefit outweighs the risks.

(6) Drug administration should begin as soon as possible after exposure to aerosolized B. anthracis. This indication is based on a surrogate endpoint. Levofloxacin plasma concentration achieved in humans is reasonably likely to predict clinical benefit (see Clinical Studies (14.6)).

(7) This regimen is indicated for (1) or (2) due to Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, and AP due to P. aeruginosa. 60 mg doses of trimethoprim-sulfamethoxazole (TMP-SMX) have been observed to be effective in pediatric patients (see Warnings and Precautions (5.10)). Use in specific Populations (5.6) and Clinical Studies (14.6).
Inhalational Anthrax (post-exposure)\(^1, \text{\textsuperscript{3}}\)

- Pediatric patients > 50 kg: 500 mg
- Pediatric patients < 50 kg and ≤ 6 months of age:
  - 8 mg/kg (not to exceed 250 mg per dose)
    - 24 hr
    - 60 days \(^5\)

Hypoge\(^4\)

- Pediatric patients > 50 kg: 500 mg
- Pediatric patients < 50 kg and ≤ 6 months of age:
  - 8 mg/kg (not to exceed 250 mg per dose)
    - 12 hr
    - 60 days \(^3\)

<table>
<thead>
<tr>
<th>Type of Infection(^*)</th>
<th>Dose</th>
<th>Freq. Once every</th>
<th>Duration(^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections in persons with a known history of multiple drug-resistant (\text{\textsuperscript{5}}) or (\text{\textsuperscript{6}}) infections, including (\text{\textsuperscript{7}}) infections, 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:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infusion reactions (including angioedema, urticaria, and erythema multiforme)</td>
<td>500 mg</td>
<td>24 hr</td>
<td>60 days (^5)</td>
</tr>
<tr>
<td>Hypersensitivity reactions</td>
<td>500 mg</td>
<td>24 hr</td>
<td>10 to 14 days</td>
</tr>
</tbody>
</table>

**2.3 Dosage Adjustment in Adults with Renal Impairment**

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

No adjustment is necessary for patients with a creatinine clearance > 50 ml/min.

In patients with impaired renal function (creatinine clearance < 50 ml/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance [see Use in Specific Populations (4.8)].

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

<table>
<thead>
<tr>
<th>Dosage in Normal Renal Function Every 24 Hours</th>
<th>Creatinine Clearance 20 to 49 ml/min</th>
<th>Creatinine Clearance 10 to 19 ml/min</th>
<th>Hemodialysis or Chronic Ambulatory Peritoneal Dialysis (CAPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>750 mg</td>
<td>750 mg every 48 hours</td>
<td>750 mg initial dose, then 500 mg every 48 hours</td>
<td>750 mg initial dose, then 500 mg every 48 hours</td>
</tr>
<tr>
<td>500 mg</td>
<td>500 mg initial dose, then 250 mg every 24 hours</td>
<td>500 mg initial dose, then 250 mg every 48 hours</td>
<td>500 mg initial dose, then 250 mg every 48 hours</td>
</tr>
<tr>
<td>250 mg</td>
<td>No dosage adjustment required</td>
<td>250 mg every 48 hours</td>
<td>No information on dosing adjustment is available</td>
</tr>
</tbody>
</table>

**2.4 Drug Interaction With Clostridium Agents: Anthrax, Saccharate, Metal Calcium, Multivitamins**

**Levosimendan Tablets**

Levosimendan tablets, USP should be administered at least two hours before or two hours after antacids containing magnesium, aluminum, as well as saccharate, metal cations such as iron, and multivitamins with iron or didanosine capsules/tablets or the pediatric formulation for oral solution [see Drug Interactions (4.3) and Patient Counseling Information (17.2)].

**2.5 Administration Instructions**

Food and Levofloxacin Tablets, USP

Levosimendan Tablets, USP can be administered without regard to food.

Hydration for Patients Receiving Levofloxacin Tablets, USP

Adequate hydration of patients receiving oral levofloxacin tablets, USP should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones [see Adverse Reactions (17.1) and Patient Counseling Information (17.3)].

**3 DOSAGE FORMS AND STRENGTHS**

TABLETS, Film coated, capsule-shaped:

- 250 mg Brownish pink tablets, debossed with “250” on one side and “C282” on the other side
- 500 mg Yellow tablets, debossed with “500” on one side and “C282” on the other side
- 750 mg White tablets, debossed with “750” on one side and “C282” on the other side

**4 CONTRAINDICATIONS**

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

**5 WARNINGS AND PRECAUTIONS**

**5.1 Tendinopathy and Tendon Rupture**

Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinopathy and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hip, the knee, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in those taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have been reported in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Levofloxacin therapy should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendonitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antibiotic. [see Adverse Reactions (6.1), Patient Counseling Information (17.3)]

**5.2 Exacerbation of Myasthenia Gravis**

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk. [see Adverse Reactions (6.1), Patient Counseling Information (17.3)]
• fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome)
• vasculitis, arthritis, myalgic serum sickness;
• allergic parameters;
• interstitial emphysema, acute renal insufficiency or failure;
• hepatic jaundice; acute hepatic necrosis or failure;
• anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia, agranulocytosis; pancytopenia, and other hematologic abnormalities.

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

5.3 Hepatotoxicity
Post-marketing reports of severe hepatotoxicity (including acute hepatic and fatal events) have been reported 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 (5.4)]. The majority of fatal hepatotoxicity reports occurred in patients 50 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see Adverse Reactions (6); Patient Counseling Information (17.3)].

5.6 Central Nervous System Effects
Convulsions, toxic psychosis, increased intracranial pressure (including pseudotumor cerebri) have been reported in patients receiving fluoroquinolones, including levofloxacin. Fluoroquinolones may also cause central nervous system stimulation which may lead to seizures, extrapyramidal symptoms, agitation, hallucinations, paranoid states, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures initiated.

5.7 Clostridium difficile-Associated Diarrhea
Clostridium difficile-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including levofloxacin, and may range in severity from mild diarrhea to severe pseudomembranous colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile. C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxinemia producing strains of C. difficile cause increased morbidity and mortality, as these infections can be fatal. To reduce the risk of CDAD, the use of antibacterial agents should be reserved for proven or suspected episodes of genuine bacterial infection (e.g., pseudomembranous colitis). CDAD must be considered in the differential diagnosis of patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

5.8 Peripheral Neuropathy
Cases of sensory or sometimes acral paresthesias affecting small and/or large areas resulting in paresthesias, hyposthesia, dysesthesia and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Symptoms may occur soon after initiation of levofloxacin and may be irreversible. Levofloxacin should be discontinued immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alteration of sensation including light touch, pain, temperature, position sense, and vibratory sensation [see Adverse Reactions (6); Patient Counseling Information (17.3)].

5.9 Prolongation of the QT Interval
Some fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes Some fluoroquinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Rare cases of torsade de pointes.
6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reactions 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.

Table 6 lists adverse reactions that have been identified during post-approval use of levofloxacin.

### Table 6: Postmarketing Reports of Adverse Drug Reactions

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Reaction</th>
<th>N=7537</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and Infestations</td>
<td>dermatitis</td>
<td>1</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>insomnia</td>
<td>4</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>headache</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>dyspnea</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>nausea</td>
<td>7</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>rash</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td>edema</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>gastrointestinal bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Reproductive and Breast Disorders</td>
<td>vaginitis</td>
<td>1</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>injection site reaction</td>
<td>1</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 cataract and multiple punctate lenticular opacities, have been noted in patients undergoing treatment with other quinolones, including levofloxacin. The relationship of the abnormalities to drug exposure is not presently established.

6.3 Postmarketing Experience

Table 6 lists adverse reactions that have been identified during post-approval use of levofloxacin. These reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.
Studies is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been evaluated. Based on human pharmacokinetics, levofloxacin is indicated in pediatric patients 6 months of age and older, for inhalational anthrax (post-exposure).

8.3 Nursing Mothers

Based on data on other fluoroquinolones and very limited data on levofloxacin, it can be presumed that the drug is excreted in human milk. Therefore, breast-feeding should be avoided during therapy with levofloxacin, and the decision to institute or continue breast-feeding should be made after carefully considering the importance of the drug to the mother.

8.1 Pregnancy

Levofloxacin was studied in two human clinical studies involving healthy volunteers while the mother was pregnant. No congenital anomalies were observed. However, since fluoroquinolones are known to cause developmental toxicity in animals, use in pregnant women is not recommended as a precautionary measure. However, in the case of potential maternal infection, the benefits of the drug should be considered in relation to any potential risks to the fetus.

8.2 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. Elevated levels of the prothrombin time in the setting of concurrent warfarin and levofloxacin have been observed with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concurrently with warfarin. Patients should also be monitored for evidence of bleeding (see Adverse Reactions (6.3)).

7.4 Non-Steroidal Anti-Inflammatory Drugs

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concurrently with fluoroquinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered (see Warnings and Precautions (5.6)).

7.5 Thiazide Diuretics

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for thiazides was demonstrated in a clinical study involving healthy volunteers. Similarly, no apparent effect of thiazides on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with thiazides has resulted in prolonged elimination half-life, elevated serum thiazide levels, and a subsequent increase in the risk of thiazide-related adverse reactions in the patient population. Therefore, thiazide levels should be closely monitored and appropriate dosage adjustment made when levofloxacin is co-administered.

7.6 Antihypertensive Agents

The concomitant administration of a non-sodium anti-inflammatory drug with a fluoroquinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures (see Warnings and Precautions (5.6)).

7 DRUG INTERACTIONS

7.1 Cholinesterase Inhibitors: Amantadine, Tacrine, Galantamine

While the cholinergic toxicity is less marked than with other fluoroquinolones, concurrent administration of levofloxacin with other agents that block cholinergic function may enhance the overall cholinergic effects. Therefore, use of levofloxacin together with agents that have anticholinergic effects should be avoided in patients with a history of increased intracranial pressure, use of anticholinergic drugs, or a recent diagnosis of uncontrolled glaucoma.

7.2 Opiates

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.

7.3 Antithrombotic Agents

There have been reports of increased bleeding in patients using anticoagulants, including warfarin, and fluoroquinolones. Therefore, patients on anticoagulants should be monitored for evidence of bleeding (see Adverse Reactions (6.3)).

7.4 Non-Steroidal Anti-Inflammatory Drugs

The concurrent administration of a non-sodium anti-inflammatory drug and a fluoroquinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures (see Warnings and Precautions (5.6)).

7.5 Thiazide Diuretics

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for thiazides was demonstrated in a clinical study involving healthy volunteers. Similarly, no apparent effect of thiazides on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with thiazides has resulted in prolonged elimination half-life, elevated serum thiazide levels, and a subsequent increase in the risk of thiazide-related adverse reactions in the patient population. Therefore, thiazide levels should be closely monitored and appropriate dosage adjustment made when levofloxacin is co-administered.

7.6 Antihypertensive Agents

The concomitant administration of a non-sodium anti-inflammatory drug with a fluoroquinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures (see Warnings and Precautions (5.6)).

7.7 Diuretics

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for diuretics was detected in a clinical study involving healthy volunteers. However, elevated serum levels of digoxin have been reported in patients with normal renal function when co-administered with other fluoroquinolones. Consequently, the AUC and t½ of digoxin were higher while CL/F absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment is required for levofloxacin or digoxin when administered concomitantly.

7.8 Probenecid and Cimetidine

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 100 mg/kg corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day corresponding to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 25 mg/kg/day corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.

These areas, however, are adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risks to the fetus.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Levofloxacin was not teratogenic in rats at oral doses as high as 110 mg/kg/day, which corresponds to 5.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 150 mg/kg corresponding to 3.0 times the highest recommended human dose based upon relative body surface area. The oral dose of 110 mg/kg/day corresponding to 5.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 25 mg/kg/day corresponding to 1.5 times the highest recommended human dose based upon relative body surface area.

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

8.3 Nursing Mothers

Based on limited data on other fluoroquinolones and very limited data on levofloxacin, it can be presumed that the drug is excreted in human milk. Therefore, breast-feeding should be avoided during therapy with levofloxacin, and the decision to institute or continue breast-feeding should be made after carefully considering the importance of the drug to the mother.

8.4 Pediatric Use

Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species (see Warnings and Precautions (5.10) and Animal Toxicology and/or Pharmacology (12.2)).

8.5 Inhalation 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 in pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been evaluated (see Indications and Usage (1.3), Dosage and Administration (2.2) and Clinical Studies (14.9)).
Levofloxacin is indicated in pediatric patients, 6 months of age and older, for treatment of plague, including pneumonic and septicemic plague due to Yersinia pestis (Y. pestis) and prophylaxis for plague.

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

### Adverse Events

#### 8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when treated with a fluoroquinolone such as levofloxacin. This risk is further increased in patients receiving concurrent corticosteroid therapy. Tendinitis or tendon rupture can affect 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.

### 8.6 Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are required following hemodialysis or CAPD (see Dosage and Administration [1.2.5]).

### 8.7 Hepatic Impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

### 10 OVERDOSAGE

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

Levofloxacin exhibits a low potential for acute toxicity. Micro, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: anemia, prostration, decreased locomotor activity, diarrhea, prostration, vomiting, and convulsions. Deaths in excess of 1300 mg/kg orally and 250 mg/kg IV produced significant mortality in calves.

### 11 DESCRIPTION

Levofloxacin, USP is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, USP is 6-fluoro-1,4-dihydro-4-oxo-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-(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 benzyl ester.

The empirical formula is C_{37}H_{37}F_N_3_O_8_S_2 + \% H_2 O and the molecular weight is 570.38.

Figure 1: The Chemical Structure of Levofloxacin

#### Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>Levofloxacin</th>
<th>Non-Fluoroquinolone</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 days</td>
<td>N = 1140</td>
<td>N = 853</td>
<td>p = 0.038</td>
</tr>
<tr>
<td>1 year²</td>
<td>46 (4.1%)</td>
<td>16 (1.9%)</td>
<td></td>
</tr>
</tbody>
</table>

* 2-sided Fisher’s Exact Test

† There were 10/46 levofloxacin-treated and 6/64 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders was calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

### 12.3 Adverse Events

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

#### 18.1.3 In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience [see Adverse Reactions (1.4)] may also be expected to occur in pediatric patients.
Levofloxacin, USP is a light yellowish-white to yellowish-crystal or crystalline powder. The molecule exists as a mixture at the pH conditions in the small intestine.

The data demonstrate that from pH 6.0 to 6.8, the solubility of levofloxacin, USP is essentially constant (approximately 100 mcg/mL). Levofloxacin, USP is considered stable to 100% in this pH range, as defined by USP procedures. Above pH 7.0, the solubility increases rapidly to its maximum at pH 7.7 (272 mcg/mL) and is considered stable to 100% in this range. Above pH 7.9, the solubility decreases and reaches a minimum value (about 50 mcg/mL) at a pH of approximately 9.5.

Levofloxacin, USP has the potential to form stable coordination compounds with many metal ions. To avoid these interactions, levofloxacin should be administered at least 1 hour before or 2 hours after eating.

Excipients and Description of Dosage Forms

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

- 250 mg (as expressed in the anhydrous form): cornstarch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Red iron oxide.
- 500 mg (as expressed in the anhydrous form): cornstarch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Yellow iron oxide.
- 750 mg (as expressed in the anhydrous form): cornstarch, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, polyethylene glycol, Povidone and Titanium dioxide.

22 CLINICAL PHARMACOLOGY

22.1 Mechanism of Action

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

22.3 Pharmacokinetics

The mean ± SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral tablet, oral solution, or intravenous (IV) doses of levofloxacin are summarized in Table 9.

![Figure 3: Mean Levofloxacin Plasma Concentration vs. Time Profile: 500mg](image)

Table 9: Mean ± SD Levofloxacin PK Parameters

<table>
<thead>
<tr>
<th>Regimen</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (mcg/mL)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>AUC&lt;sub&gt;0-t&lt;/sub&gt; (mcg·h/mL)</th>
<th>CL&lt;sub&gt;F&lt;/sub&gt; (mL/min)</th>
<th>V&lt;sub&gt;z&lt;/sub&gt; (mL)</th>
<th>V&lt;sub&gt;1&lt;/sub&gt; (mL)</th>
<th>CL&lt;sub&gt;B&lt;/sub&gt; (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg oral tablet</td>
<td>2.8 ± 0.4</td>
<td>3.6 ± 1.0</td>
<td>8.2 ± 2.7</td>
<td>18.7 ± 5.0</td>
<td>9.9 ± 2.8</td>
<td>7.0 ± 1.6</td>
<td>ND</td>
</tr>
<tr>
<td>500 mg oral tablet</td>
<td>3.9 ± 0.8</td>
<td>3.3 ± 0.6</td>
<td>47.9 ± 6.9</td>
<td>17.0 ± 8.6</td>
<td>9.4 ± 3.0</td>
<td>8.2 ± 1.4</td>
<td>ND</td>
</tr>
<tr>
<td>500 mg oral solution</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>ND</td>
</tr>
<tr>
<td>500 mg IV</td>
<td>4.2 ± 1.0</td>
<td>0.0 ± 0.0</td>
<td>48.3 ± 5.4</td>
<td>17.5 ± 1.0</td>
<td>9.0 ± 0.1</td>
<td>8.4 ± 0.7</td>
<td>ND</td>
</tr>
<tr>
<td>750 mg oral tablet*</td>
<td>0.8 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>0.8 ± 0.0</td>
<td>ND</td>
</tr>
<tr>
<td>750 mg IV #</td>
<td>3.1 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>11.5 ± 1.6</td>
<td>36.9 ± 9.0</td>
<td>15.0 ± 0.0</td>
<td>7.5 ± 0.1</td>
<td>ND</td>
</tr>
<tr>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>250 mg every 24h oral tablet</td>
<td>5.0 ± 1.4</td>
<td>3.3 ± 0.4</td>
<td>47.9 ± 6.9</td>
<td>17.0 ± 8.6</td>
<td>9.4 ± 3.0</td>
<td>8.2 ± 1.4</td>
<td>ND</td>
</tr>
<tr>
<td>500 mg every 24h oral tablet</td>
<td>4.1 ± 0.8</td>
<td>3.3 ± 0.6</td>
<td>47.9 ± 6.9</td>
<td>17.0 ± 8.6</td>
<td>9.4 ± 3.0</td>
<td>8.2 ± 1.4</td>
<td>ND</td>
</tr>
<tr>
<td>500 mg or 250 mg every 24h IV, patients with bacterial infection</td>
<td>6.7 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>72.5 ± 11.2</td>
<td>30.8 ± 9.0</td>
<td>11.0 ± 0.0</td>
<td>7.5 ± 0.1</td>
<td>ND</td>
</tr>
<tr>
<td>750 mg every 24h oral tablet</td>
<td>8.6 ± 1.3</td>
<td>3.4 ± 0.5</td>
<td>59.7 ± 17.6</td>
<td>143 ± 29</td>
<td>100 ± 10</td>
<td>8.8 ± 1.5</td>
<td>32.5 ± 20</td>
</tr>
<tr>
<td>750 mg every 24h IV</td>
<td>12.1 ± 4.1</td>
<td>3.6 ± 1.0</td>
<td>118 ± 34</td>
<td>32.0 ± 5.7</td>
<td>80 ± 20</td>
<td>7.9 ± 1.3</td>
<td>ND</td>
</tr>
<tr>
<td>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</td>
<td>5.5 ± 1.1</td>
<td>3.2 ± 0.4</td>
<td>14.8 ± 18.6</td>
<td>36.8 ± 4.4</td>
<td>9.3 ± 1.0</td>
<td>21.2 ± 38</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7.0 ± 1.3</td>
<td>3.7 ± 0.3</td>
<td>20.7 ± 34.2</td>
<td>28.6 ± 24.4</td>
<td>12.1 ± 1.6</td>
<td>21.2 ± 40</td>
<td></td>
</tr>
<tr>
<td>Young &lt;</td>
<td>5.5 ± 1.0</td>
<td>3.5 ± 0.4</td>
<td>16.7 ± 9.8</td>
<td>8.2 ± 1.0</td>
<td>9.3 ± 1.0</td>
<td>21.2 ± 38</td>
<td></td>
</tr>
<tr>
<td>Elderly</td>
<td>7.6 ± 1.6</td>
<td>3.4 ± 0.5</td>
<td>54.7 ± 28.3</td>
<td>51.2 ± 33</td>
<td>16.7 ± 9.8</td>
<td>21.2 ± 40</td>
<td></td>
</tr>
<tr>
<td>500 mg oral single dose tablet, patients with renal insufficiency:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLCR ≥50 mL/min</td>
<td>7.5 ± 1.5</td>
<td>3.5 ± 0.5</td>
<td>39.6 ± 11.8</td>
<td>80 ± 10</td>
<td>9.1 ± 0.7</td>
<td>37.8</td>
<td></td>
</tr>
<tr>
<td>CLCR 20-49 mL/min</td>
<td>7.1 ± 3.1</td>
<td>2.1 ± 1.3</td>
<td>82.1 ± 32.6</td>
<td>71.3 ± 10</td>
<td>27 ± 10</td>
<td>26 ± 13</td>
<td></td>
</tr>
<tr>
<td>CLCR &lt;20 mL/min</td>
<td>8.2 ± 2.6</td>
<td>3.1 ± 1.0</td>
<td>263.5 ± 72.5</td>
<td>73.8 ± 8</td>
<td>35.5 ± 3.3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>5.7 ± 1.0</td>
<td>2.8 ± 1.2</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>CAPD</td>
<td>6.9 ± 2.3</td>
<td>4.4 ± 1.1</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

(ND: Not determined)

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained 1 to 2 hours after oral dose. The absolute bioavailability of levofloxacin from a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin following a single intravenous dose of levofloxacin in healthy volunteers, the mean ± SD peak plasma concentration attained was 6.2 ± 1.0 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5 ± 3.0 mcg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin Oral Solutions and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily dosage regimens were approximately 5.5 ± 0.5 and 0.5 ± 0.2 mcg/mL, after the 500 mg doses, and 8.6 ± 1.5 and 1.3 ± 0.4 mcg/mL after the 750 mg doses, respectively. The mean ± SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately 0.4 ± 0.1 and 0.0 ± 0.2 mcg/mL, after the 500 mg doses, and 1.2 ± 0.1 and 1.3 ± 0.7 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500 mg dose of levofloxacin with food prolongs the time to peak concentrations by approximately 1 hour and decreases the peak concentrations by approximately 14% following tablet and approximately 22% following oral solution administration. Therefore, levofloxacin Tablets can be administered without regard to food.

The plasma concentration profile of levofloxacin after IV administration is similar in shape and magnitude to the profile observed for levofloxacin tablets when equal doses (mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.

![Figure 2: Mean Levofloxacin in Plasma Concentration vs. Time Profile: 500mg](image)

![Figure 3: Mean Levofloxacin in Plasma Concentration vs. Time Profile: 750mg](image)
Levofloxacin has Activity against microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin. Therefore, it may be active against bacteria resistant to these antimicrobials. Aminoglycosides, macrolides and β-lactam antibiotics, including penicillins. Fluoroquinolones, including levofloxacin, differ in chemical structure and mode of action from aminoglycosides, macrolides, and β-lactam antibiotics. Fluoroquinolone resistance can arise through mutations in defined regions of DNA gyrase or topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination. The mechanism of action of levofloxacin and other fluoroquinolones involves inhibition of bacterial DNA gyrase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination. The resistance of levofloxacin to spontaneous mutation in vitro is rare occurrence (rare: 10−10 to 10−14). Cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some mutants resistant to other fluoroquinolones may be susceptible to levofloxacin.

Activity in vivo Levofloxacin has in vitro activity against Gram-negative and Gram-positive bacteria.
Levofloxacin has been shown to be active against most isolates of the following bacteria in vitro and in clinical infections as described in Indications and Usage (1):

**Gram-Positive Bacteria**

*Enterococcus faecalis*

*S. aureus (methicillin-susceptible isolates)*

*S. epidermidis* (methicillin-susceptible isolates)

*S. aureus* (methicillin-resistant strains)

*S. pneumoniae* (including multi-drug resistant strains [MDRSP])

*Staphylococcus* *coagulase negative*

*Streptococcus* *pneumoniae*

† MDRSP (Multi-drug resistant Staphylococcus pneumoniae) isolates are isolates resistant to two or more of the following antibiotics: penicillin (MIC ≥2 mcg/mL), 3rd generation cephalosporins, e.g., cefoxitin; macrolides; tetracyclines; and trimethoprim/sulfamethoxazole.

**Gram-Negative Bacteria**

*Enterobacter cloacae*

*Escherichia coli*

*Haemophilus influen
tae*

*Haemophilus parainfluen
tae*

*Klebsiella pneumoniae*

*Legionella pneumophila*

*Moraxella catarrhalis*

*Pseudomonas aeruginosa*

*Providencia rettgeri*

*Proteus vulgaris*

*Proteus mirabilis*

*Proteus stuartii*

*Staphylococcus saprophyticus*

*Staphylococcus saprophyticus*

*Staphylococcus simulans*

*Staphylococcus uricata*

*Staphylococcus warneri*

*Vibrio cholerae*

**Other Bacteria**

*Chlamydophila pneumoniae*

*Mycoplasma pneumoniae*

The following in vitro data are available, but their clinical significance is unknown: levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) ≤1 mcg/mL or less against most (≥90%) isolates of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled trials.

**Gram-Positive Bacteria**

*S. aureus*

*Staphylococcus* *au
terus*

*Streptococcus* *aggregans*

*Streptococcus* *bovis*

*Streptococcus* *agalactiae*

*Streptococcus* *pyogenes*

*β-hemolytic Staphylococcus* (Group G)

*Streptococcus* *influenzae*

*Streptococcus* *oralis*

*Streptococcus* *sanguinis*

**Gram-Negative Bacteria**

*Escherichia coli*

*Haemophilus influenzae*

*Pseudomonas* *aeruginosa*

*Streptococcus* *mutans*

*Streptococcus* *sanguinis*

*Streptococcus* *sanguinis*

**Anaerobic Bacteria**

*Anaerobic Gram-Positive Bacteria*

*Clostridium perfringens*

**Susceptibility Tests**

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

**Dilution techniques:**

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using standardized procedures. Standardized procedures are based on a dilution method 1, 2, 3, 4 that has been found to be adequate for most laboratories that perform susceptibility testing. These procedures use paper disks impregnated with fixed concentrations of antimicrobial agent. The MIC values should be interpreted according to the criteria outlined in Table 9.

**Diffusion techniques:**

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure 2, 3, 4 requires the use of standardized inoculum concentrations. These procedures use paper disks impregnated with fixed concentrations of antimicrobial agent. The MIC values should be interpreted according to the criteria outlined in Table 9.

**Table 9: Susceptibility Test Interpretive Criteria for Levofloxacin**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Minimum Inhibitory Concentrations (mcg/mL)</th>
<th>Disk Diffusion (zone diameter mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S</td>
<td>I</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>S. pneumoniae</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Haemophilus parainfluenza</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>≤2</td>
<td>4</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>≤2</td>
<td>4</td>
</tr>
</tbody>
</table>

† A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermedi atere is not susceptible to the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

**Quality Control:**

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of Intermediatere is associated with an intermediate zone which permits small uncontrolled technical factors from causing major discrepancies in interpretation. A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.
Standard levofloxacin powder should provide the range of MIC concentrations for in vitro susceptibility testing. The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study. See above text for use of combination therapy.

14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in multicenter, randomized, double-blind study comparing intravenous levofloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7–15 days of levofloxacin therapy. The intravenous doses of 0.5 mg/kg/day for 7 days and intravenous doses of 60 mg/day for 4 weeks produced antipneumococcal activity. Three-month-old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe anaphylactoid syndrome resulting in the termination of dosing at Day 8 of a 14-day dosing course. N-Methyl-D-aspartate (NMDA) receptor antagonist activity in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme inhibition in vitro. When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other quinolones.

While cryoglobulin has been observed in some intravenous run studies, urinary cryoglobulin is not formed in the body, being present only after intravenous or oral administration without nephrotoxicity. In vitro animal data 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.

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

Adult patients and caregivers with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pediatric clinical studies. In the first study, 538 patients were enrolled in a prospective, multicenter, randomized, double-blind study comparing levofloxacin 500 mg once daily orally with levofloxacin 500 mg twice daily orally for a total of 7 to 14 days of levofloxacin therapy. The clinical success rate in patients receiving levofloxacin at 500 mg once daily for 7 to 14 days was significantly greater than in patients receiving levofloxacin at 500 mg twice daily for 7 to 14 days. In the second study, 254 patients were enrolled into a prospective, multicenter, noncomparative study of 500 mg levofloxacin administered orally once or twice 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%, 95%, and 70%, respectively.

Microbiologic eradication rates across both studies are presented in Table 12.

### Table 12: Bacteriologic Eradication Rates across 2 Community Acquired Pneumonia Clinical Studies

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No. Pathogens</th>
<th>Bacteriologic Eradication Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumonia</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>M. catarrhalis</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>H. influenzae</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>H. parainfluenzae</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>M. pneumoniae</td>
<td>95</td>
<td></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 resistant to two or more of the following antimicrobials: penicillin (MIC ≥ 2 mg/L), and gentamicin, cephalosporins (e.g., ceftriaxone, meropenem, and imipenem), and two or more fluoroquinolones. 34 of 40 microbiologically evaluable patients with MDRSP isolates, 30 patients (75.0%) achieved clinical and bacteriologic success at post-treatment. The clinical and bacteriologic success rates are shown in Table 13.

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

<table>
<thead>
<tr>
<th>Screening Susceptibility</th>
<th>Clinical Success</th>
<th>Bacteriologic Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin-resistant</td>
<td>16/17 (94.1%)</td>
<td>16/17 (94.1%)</td>
</tr>
<tr>
<td>2nd generation</td>
<td>30/32 (93.8%)</td>
<td>30/32 (93.8%)</td>
</tr>
<tr>
<td>Macrolide-resistant</td>
<td>28/29 (96.6%)</td>
<td>28/29 (96.6%)</td>
</tr>
<tr>
<td>Tetracycline-resistant</td>
<td>17/19 (89.5%)</td>
<td>17/19 (89.5%)</td>
</tr>
</tbody>
</table>

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

† The number of microbiologically evaluable patients where clinical success; 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 14.

### Table 14: 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>17/19 (94.1%)</td>
<td>17/19 (94.1%)</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>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>Bacteria with MDRSP</td>
<td>8/9 (89%)</td>
<td>8/9 (89%)</td>
</tr>
</tbody>
</table>

14.3 Community-Acquired Pneumonia: 3-Day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of levofloxacin, 328 patients were hospitalized adults with a clinically and radiologically determined diagnosis of 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 rate (cure plus improvement) in the clinically evaluable population was 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 (-0.5, 1.1). In the clinically evaluable population (31 days after enrollment), pneumonia was observed in 7 out of 155 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 microbiologic efficacy of the 3-day regimen was documented for infections listed in Table 15.

### Table 15: Bacteriologic Eradication Rates (Community-Acquired Pneumonia)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin 750 mg</th>
<th>Levofloxacin 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumonia</td>
<td>25/27 (92.6%)</td>
<td>26/27 (96.3%)</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>19/21 (90.5%)</td>
<td>19/21 (90.5%)</td>
</tr>
<tr>
<td>H. parainfluenzae</td>
<td>10/11 (90.9%)</td>
<td>10/11 (90.9%)</td>
</tr>
</tbody>
</table>

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

### Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin 750 mg *</th>
<th>Levofloxacin 500 mg *</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. pneumonia</td>
<td>25/27 (92.6%)</td>
<td>26/27 (96.3%)</td>
</tr>
<tr>
<td>H. influenzae</td>
<td>19/21 (90.5%)</td>
<td>19/21 (90.5%)</td>
</tr>
<tr>
<td>H. parainfluenzae</td>
<td>10/11 (90.9%)</td>
<td>10/11 (90.9%)</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.

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

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, 528 outpatient adults with clinically and radiologically determined mild to severe acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg by mouth once daily for 10 days or levofloxacin 500 mg by mouth once daily for 10 days.

Clinical success rates varied with the type of diagnosis ranging from 68% in patients with infected alar cells to 95% in patients with infected walls and abscesses. These rates were equivalent to those seen with comparator drugs.

14.5 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiologic culture results from urine

...
sample collected after prostatic massage (VP3) or expressed prostatic secretion (EPS) specimens were collected after prostatic massage (VP3) or expressed prostatic secretion (EPS) specimens. The mean plasma concentrations (563 patients). Patients with AP complicated by underlying renal diseases or conditions such as chronic obstruction, surgery, manipulation, concurrent infection or comorbid malignancies were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a bacteriologic response. The post-therapy (cure) visit occurred 10 to 14 days after the last active dose of levofloxacin and 5 to 9 days after the last dose of active ciprofloxacin. The bacteriologic cure rates overall for levofloxacin and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 18.

### Table 18: Bacteriological Eradication at Test-of-Cure

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin</th>
<th>Ciprofloxacin</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n = 165/201</td>
<td>144/165</td>
<td>-1.13 (-8.9, 6.7)</td>
</tr>
<tr>
<td>UTI</td>
<td>23/26</td>
<td>10/13</td>
<td>-2.13 (-8.9, 4.7)</td>
</tr>
<tr>
<td>cUTI</td>
<td>44/50</td>
<td>34/39</td>
<td>-0.5 (-8.9, 7.9)</td>
</tr>
<tr>
<td>N = 563</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The bacteriologic eradication rates overall for levofloxacin and control at the test-of-cure (TOC) visit for individual pathogens recovered from patients randomized to levofloxacin treatment are presented in Table 19.

### Table 19: Bacteriological Eradication Rates for Individual Pathogens Recovered From Patients Randomized to Levofloxacin 750 mg QD for 5 Days Treatment

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Bacteriological Eradication Rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococcus</td>
<td>155/197 (85.9%)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>20/23 (91.0%)</td>
</tr>
<tr>
<td>Proteus st.</td>
<td>12/13 (92.3%)</td>
</tr>
</tbody>
</table>

1. The mITT population included patients who received study medication and who had a positive (≥100 CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.

2. The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP; a cure rate (≥100 CFU/mL) at post-therapy visit at 10-14 days after the last active dose of levofloxacin, and no pathogens isolated from blood resistant to study drug, as per protocol definition or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to levofloxacin treatment are presented in Table 20.

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

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin</th>
<th>Ciprofloxacin</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>n = 164/177</td>
<td>149/167</td>
<td>-1.8 (-8.9, 5.3)</td>
</tr>
<tr>
<td>Microbiologically Evaluable Population†</td>
<td>164/177</td>
<td>149/167</td>
<td>-1.8 (-8.9, 5.3)</td>
</tr>
</tbody>
</table>

1. n = 164/177 for 38% of subjects enrolled to a protocol amendment; 5-12 days post-therapy for 72% of subjects.

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

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

### 14.3 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 chronic model of inhalational anthrax are reached or exceeded in adult and pediatric patients, receiving the recommended oral and intravenous dosage regimens (see Indications and Usage (1.13), Dosage and Administration (2.1-2.2)).

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) orally and intravenously administered plasma concentrations in human subjects receiving 500 mg orally or intravenously once daily for 5.7 ± 4.4 and 6.4 ± 6.8 microg/mL, respectively, and the corresponding total plasma exposure (AUC₀₋∞) were 47.5 ± 3.7 and 54.6 ± 11.1 microg/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from months to 17 years receiving 8 mg/kg every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable in those

### Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Levofloxacin (N=155)</th>
<th>Ciprofloxacin (N=154)</th>
<th>Overall Eradication (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>15/15 (100.0%)</td>
<td>14/15 (100.0%)</td>
<td>-0.5 (-1.9, 0.9)</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>20/20 (100.0%)</td>
<td>19/19 (100.0%)</td>
<td>-0.5 (-1.9, 0.9)</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>11/11 (100.0%)</td>
<td>10/10 (100.0%)</td>
<td>-0.5 (-1.9, 0.9)</td>
</tr>
</tbody>
</table>

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

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–10 days after completion of therapy were 75.0% for levofloxacin and 72.8% for ciprofloxacin. Clinical success rates (cure + improvement with no need for further antibiotic therapy) rates were 66.7% for the levofloxacin-treated patients and 75.0% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin.)

The overall eradication rates for pathogens of interest are presented in Table 17.
observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)].

In adults, the safety of levofloxacin for treatment duration 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 where 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 maculopapular adverse events (urticaria, urticarial, urticarial eruption, maculopapular rash, and erythema nodosum) 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 in pediatric patients is limited [see Warnings and Precautions (5.16). Use in Specific Populations (4.6)].

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 49 LD50 (range 3 to 145 LD50) of Vibrio cholerae O1 (El Tor) strain was conducted. The median inhibitory concentration (MIC) of levofloxacin for the antibiotics used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected Y1a (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 35.4 ± 3.2 mcg.h/mL. Mean (SD) steady state Cmax was 5.4 ± 0.4 mcg/mL. Morbidity due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (0%) compared to the placebo group (91%) (P<0.001, 2-sided Fisher's Exact Test). The use levofloxacin to treat 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 plague for ethical and feasibility reasons. Therefore, approval of this indication was based on antitoxin 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 plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimen [see Indications and Usage (2.2)].

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentrations in adult males receiving 500 mg orally twice daily was 5.7 ± 1.4 and 4.6 ± 0.8 mcg/mL, respectively, and the corresponding total plasma exposure (AUC0-24) was 47.5 ± 6.7 and 25.6 ± 6.1 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 was considered to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (2.3)].

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 15.5 LD50 (range 3 to 42.5 LD50) of Yersinia pestis (CO92-3132) was conducted. The median 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 50-min infusion ranged from 2.84 to 3.55 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from 0.01 to 0.05 mcg/mL. Mean (SD) AUC(0-24) was 11.9 ± 3.1 mcg.h/mL (range 9.50 to 10.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. levofloxacin or placebo beginning within one to two hours of inoculation (3.8 °C to 38 °C for more than 1 hour). Mortality in the levofloxacin group was significantly lower (1/7) 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 15 post-exposure to Y. pestis due to a gastric complication that led a blood culture positive for Y. pestis on Day 3 and all subsequent daily blood cultures from Day 4 through Day 7 were negative.

15 REFERENCES


16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Levofloxacin Tablets, USP

Levofloxacin tablets, USP 500 mg tablets are yellow, oval, bicrome, film coated tablets, debossed 500 on one side and “ZUBR” on the other side, bottles of 2 NDC:0010-3189-2 bottles of 3 NDC:0010-3189-3

Dispense in a well-closed container as defined in the USP. Use child-resistant closure (as required).

Levofloxacin tablets, USP

16.1 Levofloxacin Tablets, USP

16 HOW SUPPLIED/STORAGE AND HANDLING

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16 HOW SUPPLIED/STORAGE AND HANDLING
**Diabetes**: Diabetes is a common problem caused by antibiotics which usually ends when the antibiotics are discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (both or without stomach cramps and fever) as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physicians as soon as possible.

**Peripheral Neuropathies**: Patients should be informed that peripheral neuropathy has been associated with levofloxacin use. Symptoms may occur even after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should immediately discontinue treatment and contact their physician.

**Prolongation of the QT Interval**: Patients should be informed of any personal or family history of QT prolongation or bradycardic conditions such as long QT syndrome, heart block, or recent myocardial infarction. If they are taking any Class I (quinidine, procainamide) or Class III (amiodarone, sotalol) antiarrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

**Musculoskeletal Disorders in Pediatric Patients**: Parents should be informed that if their child has a history of joint-related problems before taking this drug, Parents of pediatric patients should also inform their child’s physician of any tendon or joint-related problems that occurred during or following levofloxacin therapy. Patients using warfarin and levofloxacin: 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. Patients should be informed that warfarin should be monitored more closely while taking levofloxacin 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.

**FDA-Approved Medication Guide**

**LEVOFLOXACIN TABLETS, USP**

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

**DISORDERS THAT CAN BE AFFECTED BY LEVOFLOXACIN**

1. **Tendon rupture or swelling of the tendon (inflammation)**
   - Tendon problems can happen in people of all ages who take levofloxacin tablets, USP. Tendons are tough cords of tissue that connect muscles to bones. Some tendon problems include pain, swelling, and inflammation of tendons including the back of the ankle (Achilles), shoulder, hand, or other tendons. Tendons are over 60 years of age.
   - Tendon problems can happen in people who do not have the above risk factors when they take levofloxacin tablets, USP.
   - Other reasons that can increase your risk of tendon problems can include:
     - Physical activity or exercise
     - Kidney failure
     - Tendon problems in the past, such as in people with rheumatoid arthritis (RA)
   - Call your healthcare provider right away at the first sign of tendon pain, swelling, or inflammation. Some tendon problems with levofloxacin tablets, USP and tendinitis or tendon rupture have been reported in patients receiving fluoroquinolone antibiotics. Patients should be informed that tendinitis or tendon rupture can happen at any time during or following levofloxacin therapy. Patients should be informed if they have any symptoms of tendon problems.
   - Tendinitis or tendon rupture can happen while you are taking or after you have finished taking levofloxacin tablets, USP. Tendinitis or tendon rupture can happen in the Achilles tendon at the back of the ankle. This is the most common area of pain and swelling. Tendons are tough cords of tissue that connect muscles to bones.
   - Get medical help right away if you get any of the following signs or symptoms of tendon rupture:
     - Tendinitis or tendon rupture:
       - Tendinitis or tendon rupture:
       - Tendinitis or tendon rupture:
       - Tendinitis or tendon rupture:
   - Levofloxacin tablets, USP are a fluoroquinolone antibiotic medicine used in adults age 18 years or older to treat certain infections caused by certain germs called bacteria. These bacterial infections include:
     - Acute respiratory tract infections.
     - Acute sinus infections.
     - Acute exacerbation of chronic bronchitis.
     - Acute bacterial skin infections.
     - Acute pelvic inflammatory disease.
     - Acute exacerbation of chronic bronchitis.
     - Acute pelvic inflammatory disease.
     - Acute respiratory tract infections.
     - Acute sinus infections.
     - Acute exacerbation of chronic bronchitis.
     - Acute bacterial skin infections.
     - Acute pelvic inflammatory disease.
   - 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, USP is also used to treat children who are 6 months of age or older and may have breathed in anthrax germs, have plague, or have been exposed to plague germs.

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

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

Who should not take levofloxacin tablets, USP?

Do not take levofloxacin tablets, USP 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, USP. See the end of this leaflet for a complete list of ingredients in levofloxacin tablets, USP.

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

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

• have tuberculosis
• have a problem that causes muscle weakness (myasthenia gravis)
• have central nervous system problem such as seizures (epilepsy)
• have nerve problems
• have or anyone in your family has uncontrolled
• heart, 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 dose lower of levofloxacin tablets, USP if your kidneys do not work well.
• have liver problems
• have diabetes or problem with low blood sugar (hypoglycemia)
• are pregnant or planning to become pregnant. It is not known if levofloxacin will harm your unborn child.
• are breastfeeding or plan to breastfeed. It is not known if levofloxacin passes into your breast milk. You and your healthcare provider should decide if you will take levofloxacin tablets, USP or breastfeed. You should not do both.

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

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

Especially tell your healthcare provider if you take:

• a central nervous system medicine
• a monoamine oxidase inhibitor (MAOI)
• a corticosteroid medicine
• a serotonin antipsychotic medicine
• a serotonin reuptake inhibitor (SSRI/SNRI)
• a tricyclic antidepressant
• a medicine to control your heart rate or blood pressure (beta-blockers)
• a medicine to treat MS
• a medicine to treat a problem that causes muscle weakness (myasthenia gravis)

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, USP?

• Take levofloxacin tablets, USP exactly as prescribed by your healthcare provider tells you to take it.
• Take levofloxacin tablets, USP at about the same time each day.
• Drink plenty of fluids while taking levofloxacin tablets, USP.
• Levofloxacin tablets, USP empty stomach or without food.
• If you miss a dose of levofloxacin tablets, USP, take it as soon as you remember. Do not take more than once in one day.
• Do not skip any doses of levofloxacin tablets, USP, or stop taking it even if you begin to feel better, until you finish your prescribed treatment, unless:
   • you have side effects. See what is the most important information I should know about levofloxacin tablets, USP.
   • your healthcare provider tells you to stop taking levofloxacin tablets, USP.

Taking all of your levofloxacin tablets, USP doses will help make sure that all of the bacteria are killed. Taking all of your levofloxacin tablets, USP doses will help you lower the chance that the bacteria will become resistant to levofloxacin tablets, USP. If your infections do not get better while you take levofloxacin tablets, USP, it may mean that the bacteria causing your infection can no longer be sensitive to levofloxacin tablets, USP. If your infection does not get better, call your healthcare provider. If your infection does not get better, levofloxacin tablets, USP and other similar antibiotic medicines may not work for you in the future.

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

What should I avoid while taking levofloxacin tablets, USP?

• Levofloxacin tablets, USP 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, USP affects you.
• Avoid sunlamps, tanning beds, and try to limit your time in the sun. Levofloxacin tablets, USP can make your skin more 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, USP, call your healthcare provider right away. You should use a sunscreen and wear a hat and clothes that cover your skin if you have to be in sunlight.

What are the possible side effects of levofloxacin tablets, USP?

Levofloxacin tablets, USP can cause serious side effects including:

• See “What Is The Most Important Information I Should Know About levofloxacin tablets, USP.”

• Serious allergic reactions.

Allergic reaction can cause people taking fluoroquinolones, including levofloxacin tablets, USP, may have a severe allergic reaction (anaphylaxis) and may be life-threatening. It may occur any time during treatment with levofloxacin tablets, USP. Call your healthcare provider 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
• dizziness, fainting
• rapid heartbeat
• skin rash

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

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

• nausea or vomiting
• stomach pain
• fever
• weakness
• abdominal pain or tenderness,
750 mg Levofloxacin Film-Coated Tablets: microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and Yellow iron Oxide.

Inactive ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate.

Active ingredient: Levofloxacin.

500 mg Levofloxacin Film-Coated Tablets: stearate, microcrystalline cellulose, polyethylene glycol, povidone, titanium dioxide and red iron oxide.

In active ingredients: corn starch, croscarmellose sodium, hypromellose, magnesium stearate.

Active ingredient: Levofloxacin.

250 mg Levofloxacin Film-Coated Tablets: yellowing of your skin or the whites of your eyes.

Stop taking levofloxacin tablets, USP and all 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, USP (a liver problem).

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

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

- Seizures
- Drowsiness, see things, or things that are not there (hallucinations)
- Feel restless
- Nervous
- Feel anxious or nervous
- Confusion
- Depression
- Trouble sleeping
- Nightmares
- Feel light-headed
- Feel more suspicious (paranoia)
- Suicide thoughts or acts
- A headache that will not go away, with or without blurry vision

Int J Mycology Drug Sensitivity
Pseudomonas aeruginosa carriages with most antibiotics, including levofloxacin tablets, USP. 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. Pseudomonas can colonize for 2 or more months after you have finished your antibiotic.

Changes in Sensation and Nerve Damage (Peripheral Neuropathy): Damage to the nerves in arms, hands, legs, or feet can happen in people taking fluoroquinolones, including levofloxacin tablets, USP. Stop levofloxacin tablets, USP and talk with your healthcare provider right away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet:

- Pain
- Burning
- Tingling
- Numbness
- Weakness

The nerve damage may be permanent.

Serious Heart Rhythm Changes (QT prolongation and ventricular tachycardia): 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, USP 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 pressure (hypotension)
- Who take certain medications to control heart rhythm (antiarrhythmics)
- Who take certain medications 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, USP.

Changes in blood sugar: People who take levofloxacin tablets, USP and other fluoroquinolone antibiotics with oral anti-diabetes medications 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, USP, stop taking levofloxacin tablets, USP and call your healthcare provider right away. Your antidiabetic medication may need to be changed.

Sensitivity to Sunlight (Photosensitivity): See “What should you avoid while taking levofloxacin tablets, USP?”

The most common side effects of levofloxacin tablets, USP include:

- Nausea
- Headache
- Diarrhea
- Insomnia
- Constipation
- Dizziness

In children 6 months and older who take levofloxacin tablets, USP to treat ear infections, dizziness is also common.

Tell your healthcare provider if you feel dizzy or faint during a treatment with levofloxacin tablets, USP.

Levofloxacin tablets, USP 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, USP. Tell your healthcare provider about any side effect that bothers you or that does not go away.

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

How should I store levofloxacin tablets, USP?
Store levofloxacin tablets, USP at 20° to 25°C (68°F to 77°F) [See USP Controlled Room Temperature].

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

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

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use levofloxacin tablets, USP for a condition for which it is not prescribed. Do not give levofloxacin tablets, USP 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, USP. If you would like more information about levofloxacin tablets, USP, talk with your healthcare provider.

You can ask your healthcare provider or pharmacist for information about levofloxacin tablets, USP that you would like more information about levofloxacin tablets, USP, talk with your healthcare provider.

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

What are the ingredients in levofloxacin tablets, USP?
- 250 mg Levofloxacin Film-Coated Tablets:
  - Active ingredient: Levofloxacin
  - 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
  - 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.

• 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.
5100 S. Dadeland Blvd., Suite 1500
Miami, Florida 33156

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Revised: 9/2015

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**LEVOFLOXACIN**
levofloxacin tablet

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**Product Characteristics**

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**Labeler**
NuCare Pharmaceuticals, Inc. (010632300)

**Establishment**

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