**LEVOFLOXACIN- levofloxacin tablet, film coated**
**DirectRX**

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**LEVOFLOXACIN**

## INDICATIONS & USAGE SECTION

- 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 to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.
  Levofloxacin tablets, USP are 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 treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin tablets, USP [see Microbiology(12.4)]. 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 will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.
  1.1 Nosocomial Pneumonia
  Levofloxacin tablets, USP are indicated for the treatment of nosocomial pneumonia due to methicillinsusceptible Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, or Streptococcus pneumoniae. Adjunctive therapy should be used as clinically indicated. Where Pseudomonas aeruginosa is a documented or presumptive pathogen, combination therapy with an antipseudomonal β-lactam is recommended [see Clinical Studies (14.1)].
  1.2 Community-Acquired Pneumonia: 7-14 day Treatment Regimen
  Levofloxacin tablets, USP are indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multidrug-resistant Streptococcus pneumoniae [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae [see Dosage and Administration (2.1) and Clinical Studies (14.2)].

  MDRSP isolates are strains resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.
  1.3 Community-Acquired Pneumonia: 5-day Treatment Regimen
  Levofloxacin tablets, USP are indicated for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae (excluding multi-drug-resistant strains [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Dosage and Administration (2.1)and Clinical Studies (14.3)].
  1.4 Acute Bacterial Sinusitis: 5-day and 10-14 day Treatment Regimens
  Levofloxacin tablets, USP are 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 are indicated for the treatment of acute bacterial exacerbation of chronic bronchitis due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis.

1.6 Complicated Skin and Skin Structure Infections

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

1.7 Uncomplicated Skin and Skin Structure Infections

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

1.8 Chronic Bacterial Prostatitis

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

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

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

1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen

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

1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen

Levofloxacin tablets, USP are 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 are 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 are 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 are based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to predict clinical benefit. Levofloxacin tablets, USP has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of levofloxacin tablets, USP in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged levofloxacin tablets, USP therapy should only be used when the benefit outweighs the risk [see Dosage and Administration(2.1, 2.2) and Clinical Studies (14.9)].

1.14 Plague

Levofloxacin tablets, USP are indicated for treatment of plague, including pneumonic and septicemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older. Efficacy studies of levofloxacin tablets, USP 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 [seeDosage and Administration (2.1, 2.2) and Clinical Studies (14.10)].

**DOSAGE & ADMINISTRATION SECTION**

- 2.1 Dosage in Adult Patients with Normal Renal Function
  The usual dose of Levofloxacin Tablet 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 dosing regimen are required [see Dosage and Administration (2.3)].
  Table 1: Dosage in Adult Patients with Normal Renal Function (creatinine clearance ≥ 50 mL/min)>

| Type of Infection* | Dosed Every 24 hours | Duration (days)† |
|---|---|---|
| Nosocomial Pneumonia | 750 mg | 7–14 |
| Community Acquired Pneumonia‡ | 500 mg | 7–14 |
| Community Acquired Pneumonia§ | 750 mg | 5 |
| Acute Bacterial Sinusitis | 750 mg | 5 |
| 500 mg | 10–14 | |
| Acute Bacterial Exacerbation of Chronic Bronchitis | 500 mg | 7 |
| Complicated Skin and Skin Structure Infections (SSSI) | 750 mg | 7–14 |
| Uncomplicated SSSI | 500 mg | 7–10 |
| Chronic Bacterial Prostatitis | 500 mg | 28 |
| Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)¶ | 750 mg | 5 |
| Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)# | 250 mg | 10 |
| Uncomplicated Urinary Tract Infection | 250 mg | 3 |
| Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg and ≥ 6 months of ageÞ,ß<br>Pediatric patients < 50 kg and ≥ 6 months of ageÞ,ß | 500 mg<br>see Table 2 below (2.2) | 60ß<br>60ß |
| Plague, adult and pediatric patients > 50 kg à<br>Pediatric patients < 50 kg and ≥ 6 months of age | 500 mg<br>see Table 2 | 10 to 14<br>10 |

| | | |
|---|---|---|
| | below (2.2) | |

*Due to the designated pathogens [see Indications and Usage (1)].†Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician.‡Due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae [see Indications and Usage (1.2)].§Due to Streptococcus pneumoniae (excluding multi-drug-resistant strains [MDRSP]), Haemophilus influenzae,Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Indications and Usage (1.3)].¶This regimen is indicated for cUTI due to Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and AP due to E. coli, including cases with concurrent bacteremia.#This regimen is indicated for cUTI due to Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa; and for AP due to E. coli.ÞDrug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized B. anthracis. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit [see Clinical Studies (14.9)].ßThe safety of levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients [see Warnings and Precautions (5.10), Use in Specific Populations (8.4), and Clinical Studies (14.9)] Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the riskàDrug administration should begin as soon as possible after suspected or confirmed exposure to Yersinia pestis. Higher doses of levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated.

## DOSAGE FORMS & STRENGTHS SECTION

TABLETS, Film-coated, capsule-shaped
250 mg pink coloured, capsule shaped, biconvex tablets debossed 'ML 62' on one side and plain on other side
500 mg peach tablets, biconvex tablets, capsule shaped, debossed 'ML 63' on one side and plain on other side
750 mg white tablets, biconvex tablets, capsule shaped, debossed 'ML 64' on one side and plain on other side

## CONTRAINDICATIONS SECTION

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

## WARNINGS AND PRECAUTIONS SECTION

- 5.1 Tendinopathy and Tendon Rupture
  Fluoroquinolones, including levofloxacin, are associated with an increased risk of tendinitis 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 hand, the biceps, the thumb, 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 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 tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug. [see Adverse Reactions ( 6.3 ); 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. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis [see Adverse Reactions (6.3); Patient Counseling Information (17.3)].

5.3 Hypersensitivity Reactions

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones, including levofloxacin. These reactions often occur following the first dose. Some reactions have been accompanied by cardiovascular collapse, hypotension/shock, seizure, loss of consciousness, tingling, angioedema (including tongue, laryngeal, throat, or facial edema/swelling), airway obstruction (including bronchospasm, shortness of breath, and acute respiratory distress), dyspnea, urticaria, itching, and other serious skin reactions. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated [see Adverse Reactions (6); Patient Counseling Information (17.3)].

5.4 Other Serious and Sometimes Fatal Reactions

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

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

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

5.5 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases

of severe hepatotoxicity were not associated with hypersensitivity [see Warnings and Precautions (5.4)]. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see Adverse Reactions (6); Patient Counseling Information (17.3)].

5.6 Central Nervous System Effects

Convulsions, toxic psychoses, 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 tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other fluoroquinolones, levofloxacin should be used with caution in patients with a known or suspected central nervous system (CNS) disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.) [see Adverse Reactions (6); Drug Interactions (7.4, 7.5); Patient Counseling Information (17.3)].

5.7 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 fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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

5.8 Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Symptoms may occur soon after initiation of levofloxacin and may be irreversible. Levofloxacin should be discontinued immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numbness, and/or weakness or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation [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 have been spontaneously reported during postmarketing surveillance in patients receiving fluoroquinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with uncorrected hypokalemia, and patients receiving ClassIA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval [see Adverse Reactions (6.3), Use in Specific Populations (8.5), and Patient Counseling Information (17.3)].

5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Levofloxacin is indicated in pediatric patients ( 6 months of age and older) only for the prevention of inhalational anthrax (post-exposure)and for plague [see Indications and Usage (1.13, 1.14)]. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin [seeUse in Specific Populations (8.4 )].

In immature rats and dogs, the oral and intravenous administration of levofloxacin resulted in increased osteochondrosis. Histopathological examination of the weight-bearing joints of immature dogs dosed with levofloxacin revealed persistent lesions of the cartilage. Other fluroquinolones also produce similar erosions in the weight-bearing joints and other signs of arthropathy in immature animals of various species [see Animal Toxicology and/or Pharmacology (13.2)].

5.11 Blood Glucose Disturbances

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

5.12 Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face, "V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of fluoroquinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs [see Adverse Reactions (6.3); Patient Counseling Information (17.3)].

5.13 Development of Drug Resistant Bacteria

Prescribing levofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria [see Patient Counseling Information (17.1)].

**ADVERSE REACTIONS SECTION**

- 6.1 Serious and Otherwise Important Adverse Reactions

  The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:
  - Tendon Effects [see Warnings and Precautions (5.1)]
  - Exacerbation of Myasthenia Gravis [see Warnings andPrecautions (5.2)]
  - Hypersensitivity Reactions [see Warnings and Precautions (5.3)]
  - Other Serious and Sometimes Fatal Reactions [see Warnings and Precautions (5.4)]
  - Hepatotoxicity [see Warnings and Precautions (5.5)]
  - Central Nervous System Effects [see Warnings andPrecautions (5.6)]
  - Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.7)]
  - Peripheral Neuropathy that may be irreversible [see Warnings and Precautions (5.8)]
  - Prolongation of the QT Interval [see Warnings and Precautions (5.9)]
  - Musculoskeletal Disorders in Pediatric Patients [see Warnings and Precautions (5.10)]
  - Blood Glucose Disturbances [see Warnings and Precautions (5.11)]
  - Photosensitivity/Phototoxicity [see Warnings and Precautions (5.12)]
  - Development of Drug Resistant Bacteria [see Warnings and Precautions (5.13)]

Crystalluria and cylindruria have been reported with quinolones, including levofloxacin. Therefore, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine [see Dosage and Administration (2.5)].

6.2 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to levofloxacin in 7537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with levofloxacin for a wide variety of infectious diseases [see Indications and Usage (1)]. Patients received levofloxacin doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3–14 days, and the mean number of days on therapy was 10 days.

The overall incidence, type and distribution of adverse reactions was similar in patients receiving levofloxacin doses of 750 mg once daily, 250 mg once daily, and 500 mg once or twice daily. Discontinuation of levofloxacin due to adverse drug reactions occurred in 4.3% of patients overall, 3.8% of patients treated with the 250 mg and 500 mg doses and 5.4% of patients treated with the 750 mg dose. The most common adverse drug reactions leading to discontinuation with the 250 and 500 mg doses were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and headache (0.2%). The most common adverse drug reactions leading to discontinuation with the 750 mg dose were gastrointestinal (1.2%), primarily nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

Adverse reactions occurring in ≥1% of levofloxacin -treated patients and less common adverse reactions, occurring in 0.1 to <1% of levofloxacin -treated patients, are shown in Table 4 and Table 5, respectively. The most common adverse drug reactions (≥3%) are nausea, headache, diarrhea, insomnia, constipation, and dizziness.

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

| **System/Organ ClassSystem/Organ Class** | **Adverse ReactionAdverse Reaction** | **% (N=7537)% (N=7537)** |
|---|---|---|
| **System/Organ Class** | **Adverse Reaction** | **% (N=7537)** |
| Infections and Infestations | moniliasis | 1 |
| Psychiatric Disorders | insomnia*[see Warnings and Precautions (5.6)] | 4 |
| Nervous System Disorders | headache<br>dizziness [see Warnings and Precautions (5.6)] | 6<br>3 |
| Respiratory, Thoracic and Mediastinal Disorders | dyspnea [see Warnings and Precautions (5.3)] | 1 |

| | | |
|---|---|---|
| Gastrointestinal Disorders | nausea<br>diarrhea<br>constipation<br>abdominal pain<br>vomiting<br>dyspepsia | 7<br>5<br>3<br>2<br>2<br>2 |
| Skin and Subcutaneous Tissue Disorders | rash [see Warnings and Precautions (5.3)]<br>pruritus | 2<br>1 |
| Reproductive System and Breast Disorders | vaginitis | 1† |
| General Disorders and Administration Site Conditions | edema<br>injection site reaction<br>chest pain | 1<br>1<br>1 |

*N=7274†N=3758 (women)

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

| System/Organ ClassSystem/Organ Class | Adverse ReactionAdverse Reaction |
|---|---|
| **System/Organ Class** | **Adverse Reaction** |
| Infections and Infestations | genital moniliasis |
| Blood and Lymphatic System Disorders | anemia<br>thrombocytopenia<br>granulocytopenia<br>[see Warnings and Precautions (5.4)] |
| Immune System Disorders | allergic reaction [See Warnings and Precautions (5.3,5.4)] |
| Metabolism and Nutrition Disorders | hyperglycemia<br>hypoglycemia<br>[see Warnings and Precautions (5.11)]<br>hyperkalemia |
| Psychiatric Disorders | anxiety<br>agitation<br>confusion<br>depression<br>hallucination<br>nightmare*<br>[see Warnings and Precautions (5.6)]<br>sleep disorder*<br>anorexia<br>abnormal dreaming* |

| | |
|---|---|
| Nervous System Disorders | tremor<br>convulsions<br>[see Warnings and Precautions (5.6)]<br>paresthesia [see Warnings and Precautions (5.8)]<br>vertigo<br>hypertonia<br>hyperkinesias<br>abnormal gait<br>somnolence*<br>syncope |
| Respiratory, Thoracic and Mediastinal Disorders | epistaxis |
| Cardiac Disorders | cardiac arrest<br>palpitation<br>ventricular tachycardia<br>ventricular arrhythmia |
| Vascular Disorders | phlebitis |
| Gastrointestinal Disorders | gastritis<br>stomatitis<br>pancreatitis<br>esophagitis<br>gastroenteritis<br>glossitis<br>pseudomembraneous/ C. difficile colitis [see Warnings and Precautions (5.7)] |
| Hepatobiliary Disorders | abnormal hepatic function<br>increased hepatic enzymes<br>increased alkaline phosphatase |
| Skin and Subcutaneous Tissue Disorders | urticaria [see Warnings and Precautions (5.3)] |
| Musculoskeletal and Connective Tissue Disorders | arthralgia<br>tendinitis<br>[see Warnings and Precautions (5.1)]<br>myalgia<br>skeletal pain |
| Renal and Urinary Disorders | abnormal renal function<br>acute renal failure [see Warnings and Precautions (5.4)] |

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

6.3 Postmarketing Experience

Table 6 lists adverse reactions that have been identified during post-approval use of levofloxacin. Because these reactions are reported voluntarily from a population of uncertain size, reliably estimating their frequency or establishing a causal relationship to drug exposure is not always possible.

Table 6: Postmarketing Reports Of Adverse Drug Reactions

| System/Organ ClassSystem/Organ Class | Adverse ReactionAdverse Reaction |
|---|---|
| **System/Organ Class** | **Adverse Reaction** |
| Blood and Lymphatic System Disorders | pancytopenia<br>aplastic anemia<br>leukopenia<br>hemolytic anemia<br>[see Warnings and Precautions (5.4)]<br>eosinophilia |
| Immune System Disorders | hypersensitivity reactions, sometimes fatal including:<br>anaphylactic/anaphylactoid reactions<br>anaphylactic shock<br>angioneurotic edema<br>serum sickness<br>[see Warnings and Precautions (5.3,5.4)] |
| Psychiatric Disorders | psychosis<br>paranoia<br>isolated reports of suicide attempt and suicidal ideation<br>[see Warnings and Precautions (5.6)] |
| Nervous System Disorders | Exacerbation of myasthenia gravis [see Warnings and Precautions (5.2)]<br>anosmia<br>ageusia<br>parosmia<br>dysgeusia<br>peripheral neuropathy (may be irreversible) [see Warnings and Precautions (5.8)]<br>isolated reports of encephalopathy<br>abnormal electroencephalogram (EEG)<br>dysphonia<br>pseudotumor cerebri [see Warning and Precautions (5.6)] |
| Eye Disorders | Uveitis<br>vision disturbance, including diplopia<br>visual acuity reduced<br>vision blurred<br>scotoma |
| Ear and Labyrinth Disorders | hypoacusis<br>tinnitus |
| Cardiac Disorders | isolated reports of torsade de pointes<br>electrocardiogram QT prolonged<br>[see Warnings and Precautions (5.9)]<br>tachycardia |

| | |
|---|---|
| Vascular Disorders | vasodilatation |
| Respiratory, Thoracic and Mediastinal Disorders | isolated reports of allergic pneumonitis [see Warnings and Precautions (5.4)] |
| Hepatobiliary Disorders | hepatic failure (including fatal cases)<br>hepatitis<br>jaundice<br>[see Warnings and Precautions 5.4, 5.5)] |
| Skin and Subcutaneous Tissue Disorders | bullous eruptions to include:<br>Stevens-Johnson Syndrome<br>toxic epidermal necrolysis<br>erythema multiforme<br>[see Warnings and Precautions (5.4)]<br>photosensitivity/photoxicity reaction [see Warnings and Precautions (5.12)]<br>leukocytoclastic vasculitis |
| Musculoskeletal and Connective Tissue Disorders | tendon rupture [see Warnings and Precautions (5.1)]<br>muscle injury, including rupture<br>rhabdomyolysis |
| Renal and Urinary Disorders | interstitial nephritis [see Warnings and Precautions (5.4)] |
| General Disorders and Administration Site Conditions | multi-organ failure<br>pyrexia |
| Investigations | prothrombin time prolonged<br>international normalized ratio prolonged<br>muscle enzymes increased |

**DRUG INTERACTIONS SECTION**

- 7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins
  Levofloxacin Tablets

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

  7.2 Warfarin

  No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for R- and S- warfarin was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of warfarin on levofloxacin absorption and disposition was observed. However, there have been reports during the postmarketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [see Adverse Reactions (6.3); Patient Counseling Information (17.4)].

  7.3 Antidiabetic Agents

Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with fluoroquinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered [see Warnings and Precautions (5.11); Adverse Reactions (6.2), Patient Counseling Information (17.4)].

7.4 Non-Steroidal Anti-Inflammatory Drugs

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

7.5 Theophylline

No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving healthy volunteers. Similarly, no apparent effect of theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other fluoroquinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels [see Warnings and Precautions (5.6)].

7.6 Cyclosporine

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

7.7 Digoxin

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for digoxin was detected in a clinical study involving healthy volunteers. Levofloxacin absorption and disposition kinetics were similar in the presence or absence of digoxin. Therefore, no dosage adjustment for levofloxacin or digoxin is required when administered concomitantly.

7.8 Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the Cmax of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t½of levofloxacin were higher while CL/F and CLR were lower during concomitant treatment of levofloxacin with probenecid or cimetidine compared to levofloxacin alone. However, these changes do not warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

7.9 Interactions with Laboratory or Diagnostic Testing

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

**USE IN SPECIFIC POPULATIONS SECTION**

- 8.1 Pregnancy

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

corresponds to 1.1 times the highest recommended human dose based upon relative body surface area, or when dosed intravenously as high as 25 mg/kg/day, corresponding to 0.5 times the highest recommended human dose based upon relative body surface area.
There are, however, no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
8.3 Nursing Mothers
Based on data on other fluoroquinolones and very limited data on levofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.
8.4 Pediatric Use
Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. [see Warnings and Precautions [5.10]and Animal Toxicology and/or Pharmacology (13.2 )]

Inhalational Anthrax (Post-Exposure)

Levofloxacin is indicated in pediatric patients 6 months of age and older, for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate. The safety of levofloxacin in pediatric patients treated for more than 14 days has not been studied [see Indications and Usage (1.13),Dosage and Administration (2.2) andClinical Studies (14.9)].

Plague

Levofloxacin is indicated in pediatric patients, 6 months of age and older, for treatment of plague, including pneumonic and septicemic plague due to Yersinia pestis (Y. pestis) and prophylaxis for plague. Efficacy studies of levofloxacin could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The risk-benefit assessment indicates that administration of levofloxacin to pediatric patients is appropriate [see Indications and Usage (1.14), Dosage and Administration (2.2) and Clinical Studies (14.10)].

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

Adverse Events

In clinical trials, 1534 children (6 months to 16 years of age) were treated with oral and intravenous levofloxacin. Children 6 months to 5 years of age received levofloxacin 10 mg/kg twice a day and children greater than 5 years of age received 10 mg/kg once a day (maximum 500 mg per day) for approximately 10 days.

A subset of children in the clinical trials (1340 levofloxacin -treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) during 60 days and 1 year following the first dose of study drug. Children treated with levofloxacin had a significantly higher incidence of musculoskeletal disorders when compared to the non-fluoroquinolone-treated children as illustrated in Table 7.

Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

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

*Non-Fluoroquinolone: ceftriaxone, amoxicillin/clavulanate, clarithromycin†There were 1199 levofloxacin s-treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit.However, the incidence of musculoskeletal disorders was calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

* Non-Fluoroquinolone: ceftriaxone, amoxicillin/clavulanate, clarithromycin
† 2-s ardless of whether they completed the 1-year evaluation visit.ided Fisher's Exact Test
‡ There were 1199 levofloxacin treated and 804 non-fluoroquinolone-treated children who had a one-year evaluation visit. However, the incidence of musculoskeletal disorders was calculated using all reported events during the specified period for all children enrolled regardless of whether they completed the 1-year evaluation visit.

Arthralgia was the most frequently occurring musculoskeletal disorder in both treatment groups. Most of the musculoskeletal disorders in both groups involved multiple weight-bearing joints. Disorders were moderate in 8/46 (17%) children and mild in 35/46 (76%) levofloxacin treated children and most were treated with analgesics. The median time to resolution was 7 days for levofloxacin -treated children and 9 for non-fluoroquinolone-treated children (approximately 80% resolved within 2 months in both groups). No child had a severe or serious disorder and all musculoskeletal disorders resolved without sequelae.
Vomiting and diarrhea were the most frequently reported adverse events, occurring in similar frequency in the levofloxacin -treated and non-fluoroquinolone-treated children.
In addition to the events reported in pediatric patients in clinical trials, events reported in adults during clinical trials or post-marketing experience [see Adverse Reactions (6)] may also be expected to occur in pediatric patients.

8.5 Geriatric Use

Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolone such as levofloxacin. This risk is further increased in patients receiving concomitant corticosteroid therapy. Tendinitis or tendon rupture can involve the Achilles, hand, shoulder, or other tendon sites and can occur during or after completion of therapy; cases occurring up to several months after fluoroquinolone treatment have been reported. Caution should be used when prescribing levofloxacin to elderly patients especially those on corticosteroids. Patients should be informed of this potential side effect and advised to discontinue levofloxacin and contact their healthcare provider if any symptoms of tendinitis or tendon rupture occur [see Boxed Warning; Warnings and Precautions (5.1); and Adverse Reactions (6.3)].

In phase 3 clinical trials, 1,945 levofloxacin -treated patients (26%) were ≥ 65 years of age. Of these, 1,081 patients (14%) were between the ages of 65 and 74 and 864 patients (12%) were 75 years or older. No overall differences in safety or effectiveness were observed between these

subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.
Severe, and sometimes fatal, cases of hepatotoxicity have been reported post-marketing in association with levofloxacin. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not associated with hypersensitivity. Levofloxacin should be discontinued immediately if the patient develops signs and symptoms of hepatitis [see Warnings and Precautions (5.5)].
Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g., Class IA or Class III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia) [see Warnings and Precautions (5.9)].

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However, since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function [see Clinical Pharmacology (12.3)].
8.6 Renal Impairment
Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance < 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD [see Dosage and Administration (2.3)].
8.7 Hepatic Impairment
Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

## OVERDOSAGE SECTION

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

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

## DESCRIPTION SECTION

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

Figure 1: The Chemical Structure of Levofloxacin USP

Structure

The empirical formula is C18H20FN3O4•½ H2O and the molecular weight is 370.38. Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a

zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin, USP is essentially constant (approximately 100 mg/mL). Levofloxacin is considered soluble to freely soluble in this pH range, as defined by USP nomenclature. Above pH 5.8, the solubility increases rapidly to its maximum at pH 6.7 (272 mg/mL) and is considered freely soluble in this range. Above pH 6.7, the solubility decreases and reaches a minimum value (about 50 mg/mL) at a pH of approximately 6.9.

Levofloxacin USP has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: Al+3>Cu+2>Zn+2>Mg+2>Ca+2.

Excipients and Description of Dosage Forms

Levofloxacin Tablets, USP

Levofloxacin Tablets, USP are available as film-coated tablets and contain the following inactive ingredients:
250 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red iron oxide.
500 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80 and synthetic red and yellow iron oxides.
750 mg (as expressed in the anhydrous form): hypromellose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80.

## CLINICAL PHARMACOLOGY SECTION

12.1 Mechanism of Action

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

12.3 Pharmacokinetics

The mean ±SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral tablet, oral solution, or intravenous (IV) doses of levofloxacin are summarized in Table 8.
Table 8: Mean ±SD Levofloxacin PK Parameters

Regimen

Cmax

Tmax

AUC

CL/F*

Vd/F†

t1/2

CLR

(mcg/mL)

(h)

(mcg·h/mL)

(mL/min)

(L)

(h)

(mL/min)

* clearance/bioavailability † volume of distribution/bioavailability ‡ healthy males 18–53 years of age § healthy males and females 19–55 years of age ¶ Absolute bioavailability; F=0.99 ± 0.08 from a 500 mg tablet and F=0.99 ± 0.06 from a 750 mg tablet; # healthy male and female subjects 18–54 years of age Þ 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose ß 500 mg every 48h for patients with moderate renal impairment (CLCR 20–50 mL/min) and infections of the respiratory tract or skin à dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling è healthy males 22–75 years of age ð healthy females 18–80 years of age ø young healthy male and female subjects 18–36 years of age ý healthy elderly male and female subjects 66–80 years of age

Single dose

250 mg oral tablet‡
2.8 ± 0.4
1.6 ± 1.0
27.2 ± 3.9
156 ± 20
ND
7.3 ± 0.9
142 ± 21

500 mg oral tablet‡
5.1 ± 0.8
1.3 ± 0.6
47.9 ± 6.8
178 ± 28
ND
6.3 ± 0.6
103 ± 30

500 mg oral solution§¶
5.8 ± 1.8
0.8 ± 0.7
47.8 ± 10.8
183 ± 40
112 ± 37.2
7.0 ± 1.4
ND

500 mg IV‡
6.2 ± 1.0
1.0 ± 0.1
48.3 ± 5.4
175 ± 20
90 ± 11
6.4 ± 0.7
112 ± 25

750 mg oral tablet#¶
9.3 ± 1.6
1.6 ± 0.8
101 ± 20
129 ± 24

83 ± 17
7.5 ± 0.9
ND

750 mg IV#
11.5 ± 4.0Þ
ND
110 ± 40
126 ± 39
75 ± 13
7.5 ± 1.6
ND

Multiple dose

500 mg every 24h oral tablet‡
5.7 ± 1.4
1.1 ± 0.4
47.5 ± 6.7
175 ± 25
102 ± 22
7.6 ± 1.6
116 ± 31

500 mg every 24h IV‡
6.4 ± 0.8
ND
54.6 ± 11.1
158 ± 29
91 ± 12
7.0 ± 0.8
99 ± 28

500 mg or 250 mg every 24h IV, patients with bacterial infectionß
8.7 ± 4.0à
ND
72.5 ± 51.2à
154 ± 72
111 ± 58
ND
ND

750 mg every 24h oral tablet#
8.6 ± 1.9
1.4 ± 0.5
90.7 ± 17.6
143 ± 29
100 ± 16
8.8 ± 1.5
116 ± 28

750 mg every 24h IV#
12.1 ± 4.1Þ
ND
108 ± 34
126 ± 37
80 ± 27

7.9 ± 1.9
ND

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

Maleè
5.5 ± 1.1
1.2 ± 0.4
54.4 ± 18.9
166 ± 44
89 ± 13
7.5 ± 2.1
126 ± 38

Femaleð
7.0 ± 1.6
1.7 ± 0.5
67.7 ± 24.2
136 ± 44
62 ± 16
6.1 ± 0.8
106 ± 40

Youngø
5.5 ± 1.0
1.5 ± 0.6
47.5 ± 9.8
182 ± 35
83 ± 18
6.0 ± 0.9
140 ± 33

Elderlyý
7.0 ± 1.6
1.4 ± 0.5
74.7 ± 23.3
121 ± 33
67 ± 19
7.6 ± 2.0
91 ± 29

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

CLCR 50–80 mL/min
7.5 ± 1.8
1.5 ± 0.5
95.6 ± 11.8
88 ± 10
ND
9.1 ± 0.9
57 ± 8

CLCR 20–49 mL/min
7.1 ± 3.1
2.1 ± 1.3
182.1 ± 62.6
51 ± 19

ND
27 ± 10
26 ± 13

CLCR <20 mL/min
8.2 ± 2.6
1.1 ± 1.0
263.5 ± 72.5
33 ± 8
ND
35 ± 5
13 ± 3

Hemodialysis
5.7 ± 1.0
2.8 ± 2.2
ND
ND
ND
76 ± 42
ND

CAPD
6.9 ± 2.3
1.4 ± 1.1
ND
ND
ND
51 ± 24
ND

ND=not determined.

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of levofloxacin from a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean ±SD peak plasma concentration attained was 6.2 ±1.0 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5 ±4.0 mcg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin Oral Solution and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7 ±1.4 and 0.5 ±0.2 mcg/mL after the 500 mg doses, and 8.6 ±1.9 and 1.1 ±0.4 mcg/mL after the 750 mg doses, respectively. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily IV regimens were approximately 6.4±0.8 and 0.6 ±0.2 mcg/mL after the 500 mg doses, and 12.1 ± 4.1 and 1.3±0.71 mcg/mL after the 750 mg doses, respectively. Oral administration of a 500 mg dose of levofloxacin tablets with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, Levofloxacin Tablets can be administered without regard to food.

The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for Levofloxacin Tablets when equal doses (mg/mg) are

administered. Therefore, the oral and IV routes of administration can be considered interchangeable (see Figure 2 and Figure 3).

Figure 2: Mean Levofloxacin Plasma Concentration vs. Time Profile: 750 mg

figure-2

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

figure-3

Distribution

The mean volume of distribution of levofloxacin generally ranges from 74 to 112 L after single and multiple 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Levofloxacin reaches its peak levels in skin tissues and in blister fluid of healthy subjects at approximately 3 hours after dosing. The skin tissue biopsy to plasma AUC ratio is approximately 2 and the blister fluid to plasma AUC ratio is approximately 1 following multiple once-daily oral administration of 750 mg and 500 mg doses of levofloxacin, respectively, to healthy subjects. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations were generally 2- to 5- fold higher than plasma concentrations and ranged from approximately 2.4 to 11.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

In vitro, over a clinically relevant range (1 to 10 mcg/mL) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied, as determined by the equilibrium dialysis method. Levofloxacin is mainly bound to serum albumin in humans. Levofloxacin binding to serum proteins is independent of the drug concentration.

Metabolism

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little relevant pharmacological activity.

Excretion

Levofloxacin is excreted largely as unchanged drug in the urine. The mean terminal plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin given orally or intravenously. The mean apparent total body clearance and renal clearance range from approximately 144 to 226 mL/min and 96 to 142 mL/min, respectively. Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving levofloxacin.

Geriatric

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 – 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary [See Use in Specific Populations (8.5)].

Pediatrics

The pharmacokinetics of levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady state plasma exposures (AUC0-24 and Cmax) to those observed in adult patients administered 500 mg of levofloxacin once every 24 hours.

Gender

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration.

Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

Race

The effect of race on levofloxacin pharmacokinetics was examined through a covariate analysis performed on data from 72 subjects: 48 white and 24 non-white. The apparent total body clearance and apparent volume of distribution were not affected by the race of the subjects.

Renal Impairment

Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in adult patients with impaired renal function (creatinine clearance< 50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD [see Dosage and Administration (2.3), Use in Specific Populations (8.6)].

Hepatic Impairment

Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment [See Use in Specific Populations (8.7)]

Bacterial Infection

The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy subjects.

Drug-Drug Interactions

The potential for pharmacokinetic drug interactions between levofloxacin and antacids warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated [see Drug Interactions (7)].

12.4 Microbiology

Mechanism of Action

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Mechanism of Resistance

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

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

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

Activity in vitro and in vivo

Levofloxacin has in vitro activity against a wide range of Gram-negative and Gram-positive bacteria.

Levofloxacin has been shown to be active against most strains of the following bacteria both in vitro and in clinical infections as described in Indications and Usage (1):

Gram-Positive Bacteria

Enterococcus faecalis
Staphylococcus aureus (methicillin-susceptible isolates)

Staphylococcus epidermidis (methicillin-susceptible isolates)

Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP]1)

Streptococcus pyogenes

Gram-Negative Bacteria

Enterobacter cloacae

Escherichia coli

Haemophilus influenzae

Haemophilus parainfluenzae

Klebsiella pneumoniae

Legionella pneumophila

Moraxella catarrhalis

Proteus mirabilis

Pseudomonas aeruginosa

Serratia marcescens

Other Bacteria

Chlamydophila pneumoniae

Mycoplasma pneumoniae

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

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

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

Gram-Positive Bacteria
Staphylococcus haemolyticus

β-hemolytic Streptococcus (Group C/F)

β - hemolytic Streptococcus (Group G)

Streptococcus agalactiae

Streptococcus milleri

Viridans group streptococci

Bacillus anthracis
Gram-Negative Bacteria

Acinetobacter baumannii

Acinetobacter lwoffii

Bordetella pertussis

Citrobacter koseri

Citrobacter freundii

Enterobacter aerogenes

Enterobacter sakazakii

Klebsiella oxytoca

Morganella morganii

Pantoea agglomerans

Proteus vulgaris

Providencia rettgeri

Providencia stuartii

Pseudomonas fluorescens

Yersinia pestis
Anaerobic Gram-Positive Bacteria
Clostridium perfringens

Susceptibility Tests

When available, the clinical microbiology laboratory should provide the results of in vitro susceptibility test results for antimicrobial drug products used in the resident hospitals to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting an antibacterial drug product for treatment.
Dilution techniques:
Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method1,2,4 (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 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 procedure2,3 requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg levofloxacin to test the susceptibility of bacteria to levofloxacin.
Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according to the criteria outlined in Table 9.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according the criteria outlined in Table 9. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

Table 9: Susceptibility Interpretive Criteria for Levofloxacin

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

Disk Diffusion
(zone diameter in mm)Disk Diffusion
(zone diameter in mm)

Pathogen

S

I

R

S

I

R

Minimum Inhibitory
Concentrations (mcg/mL)

Disk Diffusion
(zone diameter in mm)

* These interpretive standards are applicable only to broth microdilution susceptibility testing with Haemophilus influenzae and Haemophilus parainfluenzae using Haemophilus Test Medium1 † The current absence of data on resistant strains precludes defining any categories other than "Susceptible" Strains yielding MIC /zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing. ‡ These interpretive standards are applicable only to disk diffusion susceptibility testing with Haemophilus influenzae and Haemophilus parainfluenzae using Haemophilus Test Medium.2 § These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood. ¶ These zone diameter standards for Streptococcus spp. including S. pneumoniae apply only to tests performed using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO2.

Enterobacteriaceae
≤2
4
≥8
≥17
14–16
≤13

Enterococcus faecalis
≤2
4
≥8
≥17
14–16
≤13

Methicillin-susceptible Staphylococcus species
≤2
4
≥8
≥17
14–16
≤13

Pseudomonas aeruginosa
≤2
4
≥8
≥17
14–16
≤13

Haemophilus influenzae
≤2*
--†
--†
≥17‡
--†
--†

Haemophilus parainfluenzae
≤2*
--†
--†
≥17‡
--†
--†

Streptococcus pneumoniae
≤2§
4§
≥8§
≥17¶
14–16¶
≤13¶

Streptococcus pyogenes
≤2
4
≥8
≥17
14–16
≤13

S = Susceptible, I = Intermediate, R = Resistant

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

Quality Control:

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

Table 10: Quality Control for Susceptibility Testing

Microorganism

Microorganism
QC NumberMicroorganism
QC Number

MIC (mcg/mL)MIC (mcg/mL)

Disk Diffusion
(zone diameter in mm)Disk Diffusion
(zone diameter in mm)

Microorganism
QC Number

MIC (mcg/mL)

Disk Diffusion
(zone diameter in mm)

* Careful maintenance of this organism is required as the strain may lose its plasmid. † This quality control range is applicable to only H. influenzae ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM)1 ‡ This quality control range is applicable to only H. influenzae ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM)2 § This quality control range is applicable to only S. pneumoniae ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller-Hinton broth with 2–5% lysed horse blood. ¶ This quality control range is applicable to only S. pneumoniae ATCC 49619 tested by a disk diffusion procedure using Mueller-Hinton agar supplemented with 5% sheep blood and incubated in 5% CO2.

**NONCLINICAL TOXICOLOGY SECTION**

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

highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 mcg/g at Cmax.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times the highest recommended human dose based upon relative body surface area.

13.2 Animal Pharmacology & or Toxicology

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested [see Warnings and Precautions (5.10)]. In immature dogs (4–5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels.

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

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

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

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

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

## CLINICAL STUDIES SECTION

- 14.1 Nosocomial Pneumonia

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

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

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

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

| **Pathogen** | **N** | **Levofloxacin No. (%) of Patients Microbiologic/Clinical Outcomes** | **N** | **Imipenem/Cilastatin No. (%) of Patients Microbiologic/Clinical Outcomes** |
|---|---|---|---|---|
| MSSA* | 21 | 14 (66.7)/13 (61.9) | 19 | 13 (68.4)/15(78.9) |
| P. aeruginosa† | 17 | 10 (58.8)/11 (64.7) | 17 | 5 (29.4)/7 (41.2) |
| S. marcescens | 11 | 9 (81.8)/7 (63.6) | 7 | 2 (28.6)/3 (42.9) |
| E. coli | 12 | 10 (83.3)/7 (58.3) | 11 | 7 (63.6 )/8 (72.7) |
| K. pneumoniae‡ | 11 | 9 (81.8)/5 (45.5) | 7 | 6 (85.7)/3 (42.9) |
| H. influenzae | 16 | 13 (81.3)/10 (62.5) | 15 | 14 (93.3)/11(73.3) |
| S. pneumoniae | 4 | 3 (75.0)/3 (75.0) | 7 | 5 (71.4)/4 (57.1) |

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

14.2 Community-Acquired Pneumonia: 7-14 day Treatment Regimen
Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14

days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was [-6, 19]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to Chlamydophila pneumoniae, Mycoplasma pneumoniae, and Legionella pneumophila were 96%, 96%, and 70%, respectively. Microbiologic eradication rates across both studies are presented in Table 12.

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

| Pathogen | No. Pathogens | Bacteriological Eradication Rate (%) |
|---|---|---|
| H. influenzae | 55 | 98 |
| S. pneumoniae | 83 | 95 |
| S. aureus | 17 | 88 |
| M. catarrhalis | 18 | 94 |
| H. parainfluenzae | 19 | 95 |
| K. pneumoniae | 10 | 100.0 |

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

Levofloxacin was effective for the treatment of community-acquired pneumonia caused by multi-drug resistant Streptococcus pneumoniae (MDRSP). MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥2 mcg/mL), 2nd generation cephalosporins (e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patients (95.0%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 13.

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

| Screening Susceptibility | Clinical Success | Bacteriological Success* | | |
|---|---|---|---|---|
| n/N† | % | n/N‡ | % | |
| Penicillin-resistant | 16/17 | 94.1 | 16/17 | 94.1 |
| 2nd generation Cephalosporin resistant | 31/32 | 96.9 | 31/32 | 96.9 |
| Macrolide-resistant | 28/29 | 96.6 | 28/29 | 96.6 |
| Trimethoprim/ Sulfamethoxazole resistant | 17/19 | 89.5 | 17/19 | 89.5 |
| Tetracycline-resistant | 12/12 | 100 | 12/12 | 100 |

* One patient had a respiratory isolate that was resistant to tetracycline, cefuroxime, macrolides and TMP/SMX and intermediate to penicillin and a blood isolate that was intermediate to penicillin and cefuroxime and resistant to the other classes. The patient is included in the database based on respiratory isolate.
† n=the number of microbiologically evaluable patients who were clinical successes; N=number of microbiologically evaluable patients in the designated resistance group.
‡ n=the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N=number of MDRSP isolates in a designated resistance group.

Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 14.
Table 14: Clinical Success and Bacteriologic Eradication Rates for Resistant Streptococcus pneumoniae (Community Acquired Pneumonia)

| Type of Resistance | Clinical Success | Bacteriologic Eradication |
|---|---|---|
| Resistant to 2 antibacterials | 17/18 (94.4%) | 17/18 (94.4%) |
| Resistant to 3 antibacterials | 14/15 (93.3%) | 14/15 (93.3%) |
| Resistant to 4 antibacterials | 7/7 (100%) | 7/7 (100%) |
| Resistant to 5 antibacterials | 0 | 0 |
| Bacteremia with MDRSP | 8/9 (89%) | 8/9 (89%) |

14.3 Community-Acquired Pneumonia: 5-Day Treatment Regimen
To evaluate the safety and efficacy of higher dose and shorter course oflevofloxacin, 528 outpatient and hospitalized adults with clinically and radiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multicenter study comparing levofloxacin 750 mg, IV or orally, every day for five days or levofloxacin 500 mg IV or orally, every day for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in levofloxacin 750 mg group and 91.1% in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-5.9, 5.4]. In the clinically evaluable population (31–38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin 750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding cannot be determined statistically. The microbiological efficacy of the 5-day regimen was documented for infections listed in Table 15.

| Table 15: Bacteriological Eradication Rates (Community-Acquired Pneumonia) | |
|---|---|
| Penicillin susceptible S. pneumoniae | 19/20 |
| Haemophilus influenzae | 12/12 |
| Haemophilus parainfluenzae | 10/10 |
| Mycoplasma pneumoniae | 26/27 |
| Chlamydophila pneumoniae | 13/15 |

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

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

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

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

| **Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)** | | |
|---|---|---|
| **PathogenPathogen** | **Levofloxacin 750 mg×5 days Levofloxacin 750 mg×5 days** | **Levofloxacin 500 mg × 10 days Levofloxacin 500 mg × 10 days** |
| **Table 16: Clinical Success Rate by Pathogen at the TOC in Microbiologically Evaluable Subjects Who Underwent Antral Puncture (Acute Bacterial Sinusitis)** | | |
| **Pathogen** | **Levofloxacin 750 mg×5 days** | **Levofloxacin 500 mg × 10 days** |
| Streptococcus pneumoniae* | 25/27 (92.6%) | 26/27 (96.3%) |
| Haemophilus influenzae* | 19/21 (90.5%) | 25/27 (92.6%) |
| Moraxella catarrhalis* | 10/11 (90.9%) | 13/13 (100%) |

*Note: Forty percent of the subjects in this trial had specimens obtained by sinus endoscopy. The efficacy data for subjects whose specimen was obtained endoscopically were comparable to those presented in the above table.

14.5 Complicated Skin and Skin Structure Infections

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

treated patients, either shortly before or during antibiotic treatment and formed an integral part of therapy for this indication.

Among those who could be evaluated clinically 2–5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.
Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

14.6 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5–18 days after completion of therapy was 75.0% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 17.

Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

| | **Levofloxacin (N=136)** | | **Ciprofloxacin (N=125)** | |
|---|---|---|---|---|
| **Pathogen** | **N** | **Eradication** | **N** | **Eradication** |
| E. coli | 15 | 14 (93.3%) | 11 | 9 (81.8%) |
| E. faecalis | 54 | 39 (72.2%) | 44 | 33 (75.0%) |
| S. epidermidis* | 11 | 9 (81.8%) | 14 | 11 (78.6%) |

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

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

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5–18 days after completion of therapy were 75.0% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24–45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.40, 2.89] for levofloxacin minus ciprofloxacin).

14.7 Complicated Urinary Tract Infections and Acute Pyelonephritis: 5-day Treatment Regimen

To evaluate the safety and efficacy of the higher dose and shorter course of levofloxacin, 1109 patients with cUTI and AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from November 2004 to April 2006 comparing levofloxacin 750 mg IV or orally once daily for 5 days (546 patients) with ciprofloxacin 400 mg IV or 500 mg orally twice daily for 10 days (563 patients). Patients with AP complicated by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital

malformation were excluded. Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of levofloxacin and 5 to 9 days after the last dose of active ciprofloxacin.

The bacteriologic cure rates overall for levofloxacin and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 18.

Table 18: Bacteriological Eradication at Test-of-Cure

| | **Levofloxacin 750 mg orally or IV once daily for 5 days** | **Ciprofloxacin 400 mg IV/500 mg orally twice daily for 10 days** | **Overall Difference [95% CI]** | | |
|---|---|---|---|---|---|
| | **n/N** | **%** | **n/N** | **%** | **Levofloxacin Ciprofloxacin** |
| mITT Population* | | | | | |
| Overall (cUTI or AP) | 252/333 | 75.7 | 239/318 | 75.2 | 0.5 (-6.1, 7.1) |
| cUTI | 168/230 | 73.0 | 157/213 | 73.7 | |
| AP | 84/103 | 81.6 | 82/105 | 78.1 | |
| Microbiologically Evaluable Population† | | | | | |
| Overall (cUTI or AP) | 228/265 | 86.0 | 215/241 | 89.2 | -3.2 [-8.9, 2.5] |
| cUTI | 154/185 | 83.2 | 144/165 | 87.3 | |
| AP | 74/80 | 92.5 | 71/76 | 93.4 | |

*The mITT population included patients who received study medication and who had a positive (=105 CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.†The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present at = 105 CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to follow-up, and compliance with treatment (among other criteria).

Microbiologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to levofloxacin treatment are presented in Table 19.

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

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

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

14.8 Complicated Urinary Tract Infections and Acute Pyelonephritis: 10-day Treatment Regimen
To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen oflevofloxacin, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multicenter clinical trial conducted in the US from June 1993 to January 1995 comparing levofloxacin 250 orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol amendment which took place after 30% of enrollment. Microbiological efficacy was measured by bacteriologic eradication of the baseline organism(s) at 1–12 days post-therapy in patients with a pathogen identified at baseline.
The bacteriologic cure rates overall for levofloxacin and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen at baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Microbiologically Evaluable) are summarized in Table 20.

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

| | Levofloxacin 250 mg once daily for 10 days | Ciprofloxacin 500 mg twice daily for 10 days | | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| mITT Population † | 174/209 | 83.3 | 184/219 | 84.0 |
| Microbiologically Evaluable Population‡ | 164/177 | 92.7 | 159/171 | 93.0 |

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

14.9 Inhalational Anthrax (Post-Exposure)

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

Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC0-24) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)].

In adults, the safety of levofloxacin for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at 500 mg daily up to 60 days is limited. Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the risk.

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of musculoskeletal adverse events (arthralgia, arthritis, tendonopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited [see Warnings and Precautions (5.10), Use in Specific Populations (8.4)].

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD50 (~2.7 X 106) spores (range 17 - 118 LD50) of B. anthracis (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected Tmax (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 AUC0-24 was 33.4 ± 3.2 mcg.h/mL (range 30.4 to 36.0 mcg.h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post exposure was significantly lower (1/10), compared to the placebo group (9/10)

[P=0.0011, 2-sided Fisher's Exact Test]. The one levofloxacin treated animal that died of anthrax did so following the 30-day drug administration period.

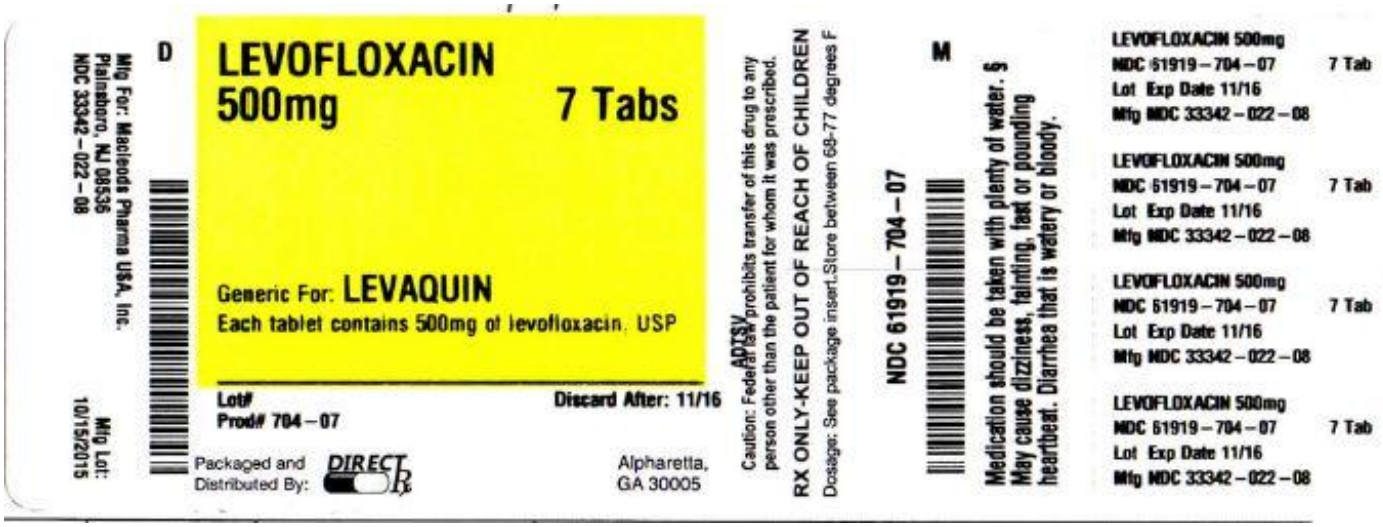
14.10 Plague

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

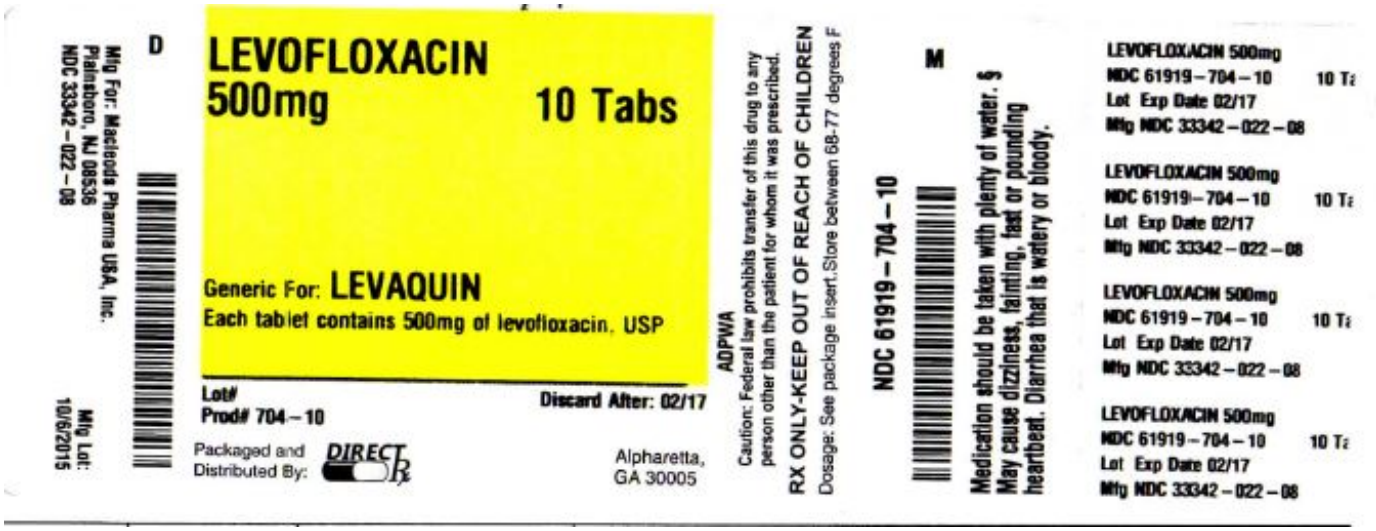
The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [see Indications and Usage (1.14), Dosage and Administration (2.1), (2.2)]. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC0-24) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg.h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)].

A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD50 (range 3 to 145 LD50) of Yersinia pestis (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the Y. pestis strain used in this study was 0.03 mcg/mL. Mean plasma concentrations of levofloxacin achieved at the end of a single 30-min infusion ranged from 2.84 to 3.50 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from <0.03 to 0.06 mcg/mL. Mean (SD) AUC0-24 was 11.9 (3.1) mcg.h/mL (range 9.50 to 16.86 mcg.h/mL). Animals were randomized to receive either a 10-day regimen of i.v. levofloxacin or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39oC for more than 1 hour). Mortality in the levofloxacin group was significantly lower (1/17) compared to the placebo group (7/7) [p<0.001, Fisher's Exact Test; exact 95% confidence interval (-99.9%, -55.5%) for the difference in mortality]. One levofloxacin-treated animal was euthanized on Day 9 post-exposure to Y. pestis due to a gastric complication; it had a blood culture positive for Y. pestis on Day 3 and all subsequent daily blood cultures from Day 4 through Day 7 were negative.

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**




**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**




# LEVOFLOXACIN

levofloxacin tablet, film coated

| Product Information | | | |
|---|---|---|---|
| **Product Type** | HUMAN PRESCRIPTION DRUG | **Item Code (Source)** | NDC:61919-704(NDC:33342-022) |
| **Route of Administration** | ORAL | | |

| Active Ingredient/Active Moiety | | |
|---|---|---|
| **Ingredient Name** | **Basis of Strength** | **Strength** |
| **LEVOFLOXACIN** (UNII: 6GNT3Y5LMF) (LEVOFLOXACIN ANHYDROUS - UNII:RIX4E89Y14) | LEVOFLOXACIN ANHYDROUS | 500 mg |

| Inactive Ingredients | |
|---|---|
| **Ingredient Name** | **Strength** |
| **CROSPOVIDONE** (UNII: 68401960MK) | |
| **CELLULOSE, MICROCRYSTALLINE** (UNII: OP1R32D61U) | |
| **MAGNESIUM STEARATE** (UNII: 70097M6I30) | |
| **TITANIUM DIOXIDE** (UNII: 15FIX9V2JP) | |
| **POLYSORBATE 80** (UNII: 6OZP39ZG8H) | |
| **FERRIC OXIDE RED** (UNII: 1K09F3G675) | |
| **FERRIC OXIDE YELLOW** (UNII: EX438O2MRT) | |
| **HYPROMELLOSES** (UNII: 3NXW29V3WO) | |
| **POLYETHYLENE GLYCOLS** (UNII: 3WQ0SDW1A) | |

| Product Characteristics | | | |
|---|---|---|---|
| **Color** | orange | **Score** | no score |
| **Shape** | capsule (capsule) | **Size** | 19mm |
| **Flavor** | | **Imprint Code** | ML;63 |
| **Contains** | | | |

## Packaging

| # | Item Code | Package Description | Marketing Start Date | Marketing End Date |
|---|---|---|---|---|
| **1** | NDC:61919-704-07 | 7 in 1 BOTTLE; Type 0: Not a Combination Product | 01/01/2015 | |
| **2** | NDC:61919-704-10 | 10 in 1 BOTTLE; Type 0: Not a Combination Product | 01/01/2015 | |

## Marketing Information

| Marketing Category | Application Number or Monograph Citation | Marketing Start Date | Marketing End Date |
|---|---|---|---|
| ANDA | ANDA200839 | 01/01/2015 | |

## Labeler - DirectRX (079254320)

## Establishment

| Name | Address | ID/FEI | Business Operations |
|---|---|---|---|
| DirectRX | | 079254320 | repack(61919-704) |

Revised: 10/2015 DirectRX