HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use LEVOFLOXACIN IN 5% DEXTROSE INJECTION safely and effectively. See full prescribing information for LEVOFLOXACIN IN 5% DEXTROSE INJECTION. LEVOFLOXACIN IN 5% DEXTROSE INJECTION, Solution for Intravenous Use Initial U.S. Approval: 1996

See full prescribing information for complete boxed warning. Fluoroquinolones, including Levofloxaci in 5% Destrose Injection, are associated with an increased risk of tendinitis and tendon upture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid dri and in patients with kidney, heart or lung transplants [see Warnings and Precautions (5.1)]. Fluoroquinolones, including Levofloxacin in 5% Dextrose Injection, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Levofloxacin in 5% Dextrose Injection in patients with a known history of myasthenia gravis [see Warnings and Precautions (5.2)].

To reduce the development of drug-resistant bacteria and maintain the effectiveness of Levofloxacin in 5% Dextrose Injection and other ntibacterial drugs, Levofloxacin in 5% Dextrose Injection should be used only to treat or prevent infections that are proven or strongly suspected

---INDICATIONS AND USAGE-----Levofloxacin in 5% Dextrose Injection is a fluoroquinolone antibacterial indicated in adults (≥ 18 years of age) with infections caused by

 Acute bacterial sinusitis (1.4)
 Acute bacterial exacerbation of chronic bronchitis (1.5) Skin and skin structure infections: complicated (1.6) and uncomplicated (1.7) Chronic bacterial prostatitis (1.8) Virinary tract infections: complicated (1.9, 1.10) and uncomplicated (1.12)
 Acute pyelonephritis (1.11) Inhalational anthrax, post-exposure (1.13) Plague (1.14) ---DOSAGE AND ADMINISTRATION---

• Dosage in patients with normal renal function (2.1)

Dilute single-use vials to 5 mg/mL prior to IV infusion (2.6)
Do not mix with other medications in vial or IV line (2.6)

**FULL PRESCRIBING INFORMATION: CONTENTS\*** 

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1.13 Inhalational Anthrax (Post-Exposure)

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Tendinopathy and Tendon Rupture Exacerbation of Myasthenia Gravis

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Complicated Skin and Skin Structure Infections

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Community-Acquired Pneumonia: 5-day Treatment Regimen
Acute Bacterial Sinusitis: 5-day and 10 to 14 day Treatment Regimen
Acute Bacterial Exacerbation of Chronic Bronchitis

INDICATIONS AND USAGE

Nosocomial Pneumonia

	24 hours	(days)
Nosocomial Pneumonia (1.1)	750 mg	7 to 14
Community-Acquired Pneumonia (1.2)	500 mg	7 to 14
Community-Acquired Pneumonia (1.3)	750 mg	5
Acute Bacterial Sinusitis (1.4)	750 mg	5
	500 mg	10 to 14
Acute Bacterial Exacerbation of Chronic Bronchitis (1.5)	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI) (1.6)	750 mg	7 to 14
Uncomplicated SSSI (1.7)	500 mg	7 to 10
Chronic Bacterial Prostatitis (1.8)	500 mg	28
Complicated Urinary Tract Infection (1.9) or Acute Pyelonephritis (1.11)	750 mg	5
Complicated Urinary Tract Infection (1.10) or Acute Pyelonephritis (1.11)	250 mg	10
Uncomplicated Urinary Tract Infection (1.12)	250 mg	3
Inhalational Anthrax (Post-Exposure) (1.13)		
Adults and Pediatric Patients > 50 kg	500 mg 8 mg/kg BID (not to exceed	60
Pediatric Patients < 50 kg and ≥ 6 months of age	250 mg/dose)	60
Plague (1.14)		
Adults and Pediatric Patients > 50 kg	500 mg	10 to 14
Pediatric Patients < 50 kg and ≥ 6 months of age	8 mg/kg BID (not to exceed 250 mg/dose)	10 to 14

1.8 Chronic Bacterial Prostatitis

-1.9 - Cemplicated Urinary-Tract Infections: 5-day-Treatment-Regimen-

Dose Every

Duration

----DOSAGE FORMS AND STRENGTHS----Injection: premix single-use flexible containers 250 mg in 50 m 500 mg in 100 mL

Known hypersensitivity to Levofloxacin in 5% Dextrose Injection or other quinolones (4, 5.3).

Risk of tendinitis and tendon rupture is increased. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs (5.1, 8.5)
May exacerbate muscle weakness in persons with myasthenia gravis. Avoid use in patients with a known history of myasthenia gravis (5.2)
Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose (4, 5.3)

Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.4) Hepatotoxicity: Severe, and sometimes fatal, hepatotoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur (5.5) Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. Increased intracranial pressure (pseudotumor cerebri) has been reported (5.6) Clostridium difficile-associated colitis: evaluate if diarrhea occurs (5.7) athy: discontinue immediately if symptoms occur in order to prevent irreversibility (5.8)

Prolongation of the QT interval and isolated cases of torsades de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalemia, and with other drugs that prolong the QT interval (5.9, 8.5)

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC, Vigilance & Medical Affairs at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch. ---DRUG INTERACTIONS----

Interacting Drug Absorption of levofloxacin is decreased when the tablet or oral solution formulation is taken within 2 hours products including antacids, f these products. Do not co-administer the intravenous formulation in the same IV line with a multivalent cation, e.g., magnesium (2.4, 7.1) metal cations or didanosine Effect may be enhanced. Monitor prothre Carefully monitor blood glucose (5.11, 7.3 ----USE IN SPECIFIC POPULATIONS---

Geriatrics: Severe hepatotoxicity has been reported. The majority of reports describe patients 65 years of age or older (5.5, 8.5, 17). May have certaints: Severe reparticularly last been reported. The highing or reports describe patients of years or age or older (3.3, 6.3, 17). May have increased risk of tendinopathy (including rupture), especially with concomitant corticosteroid use (5.1, 8.5, 17). May be more susceptible to prolongation of the QT interval (5.9, 8.5, 17).

Pediatrics: Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen in more levofloxacin-treated patients than in comparator. Shown to cause arthropathy and osteochondrosis in juvenile animals (5.10, 8.4, 13.2). Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (post-exposure) (1.13, 2.2, 8.4, 14.9) and

See 17 for PATIENT COUNSELING INFORMATION and the FDA-approved Medication Guide.

Revised: March 2015

Type of Infection\*

Pediatric patients > 50 kg

ational Anthrax (post-exposure)

01-59-12-002B

Digoxin
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 14.5 Complicated Skin and Skin Structure Infections
 14.6 Chronic Bacterial Prostatitis
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Pediatric Patients and Arthropathic Effects in Animals

Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins

7 DRUG INTERACTIONS Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins Warfarin Anti-diabetic Agents 7.4 Non-Steroidal Anti-Inflammatory Drugs 7.5 Theophylline

FULL PRESCRIBING INFORMATION WARNING: Fluoroquinolones, including Levofloxacin in 5% Dextrose Injection, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs and in patients with kidney, heart or lung transplants [see Warnings and Precautions (5.1)].

Fluoroquinolones, including Levofloxacin in 5% Dextrose Injection, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid Levofloxacin in 5% Dextrose Injection in patients with a known history of myasthenia gravis [see Warnings and 1 INDICATIONS AND USAGE To reduce the development of drug-resistant bacteria and maintain the effectiveness of levofloxacin in 5% dextrose injection and other antibacterial drugs, levofloxacin in 5% dextrose injection 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

Levofloxacin in 5% dextrose injection is indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible isolates of the designated microorganisms in the conditions listed in this section. Levofloxacin in 5% dextrose injection is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral

Culture and susceptibility testing

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin [see Microbiology (12.4)]. Therapy with levofloxacin may be initiated before results of these ests are known; once results become available, appropriate therapy should be selected As with other drugs in this class, some isolates of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with

levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance. Levofloxacin is indicated for the treatment of nosocomial pneumonia due to methicillin-susceptible Staphylococcus aureus. Pseudomonas

Levoluxacin's indicated of the realinent or indexocurinal prientinina due to the interminant of the intermi 1.2 Community-Acquired Pneumonia: 7 to 14 day Treatment Regimen Levofloxacin is indicated for the treatment of community-acquired pneumonia due to methicillin-susceptible Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug-resistant Streptococcus pneumoniae [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae

[see Dosage and Administration (2.1) and Clinical Studies (14.2)]. MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥ 2 mcg/mL), 2<sup>nd</sup> generation cephalosporins, 1.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

1.3 Community-Acquirred Prelumonia: 3-day Ireatment Regimen Levrofloxacin is indicated for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae (excluding multi-drug-resistant isolates [MDRSP]), Haemophillus influenzae, Haemophillus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Dosage and Administration (2.1) and Clinical Studies (14.3)1. 1.4 Acute Bacterial Sinusitis: 5-day and 10 to 14 day Treatment Regimens
Levofloxacin is indicated for the treatment of acute bacterial sinusitis due to Streptococcus pneumoniae, Haemophillus influenzae, or Moraxella catarrhalis [see Clinical Studies (14.4)].

1.5 Acute Bacterial Exacerbation of Chronic Bronchiti Levofloxacin is 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

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 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
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16.1 Levofloxacin Injection Pre-Mixed Solution, Single-Use in Flexible Container

 50 Bod Survey Common Control of \*Sections or subsections omitted from the full prescribing information are not listed.

1.6 Complicated Skin and Skin Structure Infections Levofloxacin is indicated for the treatment of complicated skin and skin structure infections due to methicillin-susceptible Staphylococcus aureus.

ccus faecalis, Streptococcus pyogenes, or Proteus mirabilis [see Clinical Studies (14.5)]. 1.7 Uncomplicated Skin and Skin Structure Infections Levofloxacin is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible Staphylococcus aureus, or Streptococcus pyogen

Levofloxacin is indicated for the treatment of chronic bacterial prostatitis due to Escherichia coli, Enterococcus faecalis, or methicillin-susceptible Staphylococcus epidermidis [see Clinical Studies (14.6)]. evofloxacin is indicated for the treatment of complicated urinary tract infections due to Escherichia coli. Klebsiella pneumoniae, or Proteus mirabilis [see Clinical Studies (14.7)].

1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen Levofloxacin is indicated for the treatment of complicated urinary tract infections (mild to moderate) due to Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, or Pseudomonas aeruginosa [see Clinical Studies (14.8)]. 1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen
Levofloxacin is indicated for the treatment of acute pyelonephritis caused by Escherichia coli, including cases with concurrent bacteremia [see Clinical

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

evofloxacin is indicated for inhalational anthrax (post-exposure) to reduce the incidence or progression of disease following exposure to aerosolized

Bacillus anthracis. The effectiveness of levofloxacin is based on plasma concentrations achieved in humans, a surrogate endpoint reasonably likely to

predict clinical benefit. Levofloxacin has not been tested in humans for the post-exposure prevention of inhalation anthrax. The safety of levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations of therapy beyond 14 days has not been studied. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk [see Dosage and Administration (2.1, 2.2) and Clinical Studies (14.9)]. evofloxacin is indicated for treatment of plague, including pneumonic and septicemic plague, due to Yersinia pestis (Y. pestis) and prophylaxis for plague in adults and pediatric patients, 6 months of age and older. Efficacy studies of levofloxacin could not be conducted in humans with plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy studies type the conducted in humans with plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals [see Dosage and

Administration (2.1, 2.2) and Clinical Studies (14.10)]. 2 DOSAGE AND ADMINISTRATION 2.1 Dosage in Adult Patients with Normal Renal Function The usual dose of levofloxacin in 5% dextrose injection is 250 mg or 500 mg administered by slow infusion over 60 minutes every 24 hours or 750 mg

stered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in Table hese 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\* 7 to 14 Community-Acquired Pneumonia 500 mg nmunity-Acquired Pneumonia 750 mg 750 mg 10 to 14 500 mg Acute Bacterial Exacerbation of Chronic Bronchitis 500 mg Complicated Skin and Skin Structure Infections (SSSI) 750 mg hronic Bacterial Prostatiti 500 mg complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (A 750 mg 250 mg alational Anthrax (Post-Exposure), adult and pediatric patients > 50 kgb Pediatric patients < 50 kg and ≥ 6 months of age<sup>b,t</sup> see Table 2 below (2.2) Plague, adult and pediatric patients > 50 kg° Pediatric patients < 50 kg and ≥ 6 months of age See Table 2 below (2.2)

Due to the designated pathogens [see Indications and Usage (1)] equential therapy (intravenous to oral) may be instituted at the discretion of the physician Due to methicillin-susceptible Staphylococcus aureus. Streptococcus pneumoniae (including multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae [see Indications and Usage (1.2)]. Due to Strentococcus pneumoniae (excluding multi-drug-resistant isolates (MDRSPI). 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 This regimen is indicated for cUTI due to Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, nonas aeruginosa; and for AP due to E. coli. Pseudomonas aeruginosa; and for AP due to E. coli.

Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized B. anthracis. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit [see Clinical] The safety of levofloxacin in adults for durations of therapy beyond 28 days or in pediatric patients for durations beyond 14 days has not been

studied. An increased incidence of musculoskeletal adverse events compared to controls has been observed in pediatric patients [see Warnings and Precautions (5.10), Use in Specific Populations (8.4) and Clinical Studies (14.9)]. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk. Drug administration should begin as soon as possible after suspected or confirmed exposure to Yersinia pestis. Higher doses of levofloxacin typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated 2.2 Dosage in Pediatric Patients The dosage in pediatric patients ≥ 6 months of age is described below in Table 2.

Table 2: Dosage in Pediatric Patients ≥ 6 months of age

500 mg

Freq. Once Every

24 hr

Duration<sup>†</sup>

60 days§

60 days§

Pediatric patients < 50 kg and ≥ 6 months of age 8 mg/kg (not to exceed 250 mg per dose) 12 hr Pediatric patients > 50 kg 10 to 14 days Pediatric patients < 50 kg and ≥ 6 months of age 12 hr

8 mg/kg (not to exceed 250 mg per dose 10 to 14 days Due to Bacillus anthracis [see Indications and Usage (1.13)] and Yersinia pestis [see Indications and Usage (1.14)]. Sequential therapy (intravenous to oral) may be instituted at the discretion of the physician. Drug administration should begin as soon as possible after suspected or confirmed exposure to aerosolized B. anthracis. This indication is based on a surrogate endpoint. Levofloxacin plasma concentrations achieved in humans are reasonably likely to predict clinical benefit [see Clinical Studies (14.9)].
The safety of levofloxacin in pediatric patients for durations of therapy beyond 14 days has not been studied. An increased incidence of

musculoskeletal adverse events compared to controls has been observed in pediatric patients [see Warnings and Precautions (5.10), Use in Specific Populations (8.4) and Clinical Studies (14.9)]. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk. Drug administration should begin as soon as possible after suspected or confirmed exposure to Yersinia pestis. 2.3 Dosage Adjustment in Adults with Renal Impairment 2.3 Dosage Agustinent in Adults with retrai impairment Administer levolfoxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levolfoxacin may be reduced.

No adjustment is necessary for patients with a creatinine clearance ≥ 50 mL/min. In patients with impaired renal function (creatinine clearance < 50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of vofloxacin due to decreased clearance [see Use in Specific Populations (8.6)] Table 3 shows how to adjust dose based on creatinine clearance.

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

Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (creatinine clearance < 50 mL/min)

2.4 Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins in in 5% dextrose injection should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line (see Dosage and Administration (2.6)).

Caution: Rapid or bolus intravenous infusion of levofloxacin has been associated with hypotension and must be avoided. Levofloxacin in 5% dextrose \_injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. Levofloxacio in 5% dextrose.

Hydration for Patients Receiving Levofloxacin in 5% Dextrose Injection Adequate hydration of patients receiving intravenous levofloxacin should be maintained to prevent the formation of highly concentrated urine. Crystalluria and cylindruria have been reported with quinolones [see Adverse Reactions (6.1) and Patient Counseling Information (17.2)].

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container Because only limited data are available on the compatibility of levofloxacin in 5% dextrose injection with other intravenous substances, additives or other medications should not be added to Levofloxacin Injection Premix Solution in Single-Use Flexible Containers or infused simultaneously through the

same intravenous line. If the same intravenous line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of levofloxacin in 5% dextrose injection with an infusion solution compatible with levofloxacin in 5% dextrose injection and with any other drug(s) Levofloxacin Injection Premix in Single-Use Flexible Containers (5 mg/mL)

Levofloxacin in 15% destrose injection is supplied in flexible containers within a foil overwrap. These contain a premixed, ready to use levofloxacin solution in 5% dextrose (D5W) for single-use. The 50 mL premixed flexible container contains 250 mg/50 mL of levofloxacin solution. The 100 mL premixed flexible container contains 500 mg/100 mL of levofloxacin solution. The 150 mL premixed flexible container contains 750 mg/150 mL of evofloxacin solution. The concentration of each container is 5 mg/mL. No further dilution of these preparations is necessary. Because the premix flexible containers are for single-use only, any unused portion should be discarded Instructions for the Use of Levofloxacin Injection Premix in Single-Use Flexible Containers:

 Tear outer wrap at the notch and remove solution container.
 Check the container for minute leaks by squeezing the inner bag firmly. If leaks are found, or if the seal is not intact, discard the solution, as the sterility may be compromised.

3. Do not use if the solution is cloudy or a precipitate is present. 5. WARNING: Do not admix with other drugs or additives. Such use could result in air embolism due to residual air being drawn from ation of the fluid from the secondary container is complet

Preparation for Administration:

1. Close flow control clamp of administration set. Remove cover from port at bottom of container.
 Insert piercing pin of administration set into port with a twisting motion until the pin is firmly seated. NOTE: See full directions on administration set carton. 4. Suspend container from hanger.

5. Squeeze and release drip chamber to establish proper fluid level in chamber during infusion of Levofloxacin Injection Premix in Flexible Containers. Open flow control clamp to expel air from set. Close clamp.

Regulate rate of administration with flow control clamp. 3 DOSAGE FORMS AND STRENGTHS

evofloxacin in 5% dextrose injection is supplied in single-use flexible containers for intravenous infusion, and is clear yellow to clear greenish-yellow in

appearance. 250 mg, in flexible container, 50 mL fill 500 mg, in flexible container, 100 mL fill
750 mg, in flexible container, 150 mL fill 4 CONTRAINDICATIONS cacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibacterials [see Warnings and Precautions

5 WARNINGS AND PRECAUTIONS

luoroquinolones, 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) and Patient Counseling Information (17.3)].

5.2 Evacerhation of Myaethenia Gravis uoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing 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) and Patient

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroguinolones. 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, antihistamine corticosteroids, pressor amines, and airway management, as clinically indicated [see Adverse Reactions (6) and 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 natients

• 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.

receiving therapy with fluoroquinolones, including levofloxacin. These events may be severe and generally occur following the add doses. Clinical manifestations may include one or more of the following:

The drug should be discontinued immediately at the first appearance of skin rash, jaundice, or any other sign of hypersensitivity and supportive easures instituted [see Adverse Reactions (6) and Patient Counseling Information (17.3 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) and 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, rightmares, 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 (fig. Drug Interactions 7, 4 7, 5] and Patient Counseling Information (17, 31) (6). Drug Interactions (7.4, 7.5) and 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) and Patient Counseling Information (17.3)].

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) and 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 torsades de pointes have been spontaneously reported during post-marketing surveillance in patients receiving fluoroquinolones, including levofloxacin. Levofloxacin should be avoided in patients with known prolongation of the QT interval, patients with

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and

uncorrected hypokalemia, and patients receiving Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) antiarrhythmic agents. Elderly patients may be more susceptible to drug-associated effects on the QT interval [see Adverse Reactions (6.3), Use in Specific Populations (8.5) and 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 (arthratgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin [see Use in Specific Populations (8.4)].

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

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, bilstering, 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, expossive to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs [see Adverse Reactions (6.3) and Patient

discontinued and appropriate therapy should be initiated immediately [see Adverse Reactions (6.2), Drug Interactions (7.3) and Patient Counseling

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)]

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)]

I lendon Effects (see Warnings and Precautions (5.1)]
Exacerbation of Myasthenia Gravis (see Warnings and Precautions (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 and Precautions (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)]

6 ADVERSE REACTIONS

Hypotension has been associated with rapid or bolus intravenous infusion of levofloxacin. Levofloxacin should be infused slowly over 60 to 90 minutes depending on dosage [see Dosage and Administration (2.5)]. 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 7,537 patients in 29 pooled Phase 3 clinical trials. The population studied had a mean age of 50 years (approximately 74% of the population was < 65 years of age), 50% were male, 71% were Caucasian, 19% were Black. Patients were treated with levofloxacin for a wide variety of infectious diseases [see Indications and Usage (1)]. Patients received levofloxacin doses of 750 mg once daily, 250 mg once daily, or 500 mg once or twice daily. Treatment duration was usually 3 to 14 days, and the mean number of days on therapy was 10

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 250 mg dose. The most common adverse drug reactions, a 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,

Table 4: Common (≥ 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin % (N = 7,537) System/Organ Class Adverse Reaction **Psychiatric Disorders** insomnia\* [see Warnings and Precautions (5.6)] headache fizziness [see Warnings and Precautions (5.6)] Respiratory, Thoracic and Mediastinal Disorders dyspnea [see Warnings and Precautions (5.3)] diarrhea constipation rash [see Warnings and Precautions (5.3)] vaginitis General Disorders and Administration Sit injection site reaction

† N = 3,758 (women)

Table 5: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin (N=7.537) System/Organ Class Infections and Infestation genital moniliasis **Blood and Lymphatic System Disorder** anemia thrombocytopenia [see Warnings and Precautions (5.4)] allergic reaction [see Warnings and Precautions (5.3, 5.4)] Immune System Disorders Metabolism and Nutrition Disorders hyperglycemia hypoglycemia
[see Warnings and Precautions (5.11)] anxiety Isee Warnings and Precautions (5.6)1 abnormal dreaming Isee Warnings and Precautions (5.6)1 paresthesia [see Warnings and Precautions (5.8)] hypertonia abnormal gait syncope Respiratory, Thoracic and Mediastinal Disorders cardiac arrest palpitation ventricular tachycard ventricular arrhythmia Vascular Disorders pancreatitis esophagitis pseudomembranous/C. difficile colitis [see Warnings and Precautions (5.7)] abnormal hepatic function increased hepatic enzymes Skin and Subcutaneous Tissue Disorders urticaria [see Warnings and Precautions (5.3)] Musculoskeletal and Connective Tissue Disorders arthralgia [see Warnings and Precautions (5.1)] myalgia skeletal pain Renal and Urinary Disorders abnormal renal function acute renal failure [see Warnings and Precautions (5.4)] N = 7.274

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 6.3 Post-marketing 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

Table 6: Post-marketing Reports of Adverse Drug Reactions System/Organ Class aplastic anemia hemolytic anemia anaphylactic shock angioneurotic edema [see Warnings and Precautions (5.3, 5.4)] isolated reports of suicide attempt and suicidal ideation exacerbation of myasthenia gravis [see Warnings and Precautions peripheral neuropathy (may be irreversible) [see Warnings and Precautions (5.8)1 isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudotumor cerebri [see Warnings and Precautions (5.6)] Eve Disorders vision disturbance, including diplopia visual acuity reduced vision blurred scotoma tinnitus Cardiac Disorders isolated reports of torsades de pointes electrocardiogram QT prolonged [see Warnings and Precautions (5.9)] Vascular Disorders Respiratory, Thoracic and Mediastinal Disorders isolated reports of allergic pneumonitis [see Warnings and Precautions (5.4)] epatobiliary Disorders hepatic failure (including fatal cases) [see Warnings and Precautions (5.4, 5.5)] Skin and Subcutaneous Tissue Disorders bullous eruptions to include: Stevens-Johnson Syndrome toxic epidermal necrolysis erythema multiforme [see Warnings and Precautions (5.4)] photosensitivity/phototoxicity reaction [see Warnings and Precautions (5.12)] eukocytoclastic vasculitis sculoskeletal and Connective Tissue Disorder tendon rupture [see Warnings and Precautions (5.1)] muscle injury, including rupture Renal and Urinary Disorders interstitial nephritis [see Warnings and Precautions (5.4)] General Disorders and Administration Site Condition multi-organ failure nvestigations prothrombin time prolonged international normalized ratio prolonged

7 DRUG INTERACTIONS

7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins
There are no data concerning an interaction of intravenous fluoroquinolones with oral antacids, sucralfate, multivitamins, didanosine, or metal cations. However, no fluoroquinolone should be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line [see Dosage and Administration (2.5)].

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 post-marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of the prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, International Normalized Ratio (INR), or other suitable anticoagulation tests should be closely monitored if levofloxacin is administered concomitantly with warfarin. Patients should also be monitored for evidence of bleeding [see Adverse Reactions (6.3) and Patient Counseling Information (17.4)1. 7.3 Anti-diabetic Agents Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with

fluoroquinolones and an anti-diabetic 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) and Patient Counseling Information (17.4)]. 7.4 Non-Steroidal Anti-Inflammatory Drugs The concomitant administration of a non-steroidal anti-inflammatory drug with a fluoroguinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures [see Warnings and Precautions (5.6)].

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 levelfoxacin is co-administered. Adverse reactions, including seizures, may occur with or without an elevation in serum theophylline levels (see Warnings and Precautions (5.61).

No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other fluoroquinolones. Levofloxacin C \_\_ and k, were slightly lower while T\_\_ and t, were slightly longer in the presence of cyclosporine than those observed in other studies without concenitant 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 linical 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.

No significant effect of probenecid or cimetidine on the C<sub>max</sub> of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t<sub>w</sub> of levofloxacin were higher while CL/F and Cl<sub>m</sub> were lower during concomitant treatment of levofloxacin with probenecid or cimetidine compared to levofloxacin alone. However, these changes do not warrant dosage adjustment for levofloxacin when probenecid or cimetidine is

7.9 Interactions with Laboratory or Diagnostic Testing Some fluoroguinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available munoassay kits. Confirmation of positive opiate screens by more specific methods may be necessary 8 USE IN SPECIFIC POPULATIONS

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

Based on data on other fluoroguinolones 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. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species [see Warnings and Precautions

Pharmacokinetics following intravenous administration

The pharmacokinetics of levofloxacin following a single intravenous dose were investigated in pediatric patients ranging in age from six 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 [see Clinical Pharmacology (12.3) and Clinical Studies (14.9)]. Inhalational Anthrax (Post-Exposure)

patients 6 months of age and older, for inhalational anthrax (post-exposure). The risk-benefit assessment xacin to pediatric patients is appropriate. The safety of levol than 14 days has not been studied [see Indications and Usage (1.13), Dosage and Administration (2.2) and Clinical Studies (14.9)].

Levofloxacin is indicated in pediatric patients, 6 months of age and older, for treatment of plague, including pneumonic and septicemic plague due to Yersinia pestis (Y. pestis) and prophylaxis for plague. 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 sment indicates that administration of levofloxacin to pediatric patients is appropriate [see Indications and Usage (1.14), Dosage and

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

Adverse Events.
In clinical trials, 1,534 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 (1,340 levofloxacin-treated and 893 non-fluoroquinolone-treated) enrolled in a prospective, long-term surveillance study to assess the incidence of protocol-defined musculoskeletal disorders (arthralgia, arthritis, tendinopathy, gait abnormality) during 60 days and 1 year following the first dose of the study drug. Children treated with levofloxacin had a significantly higher incidence of

nusculoskeletal disorders when compared to the non-fluoroguinolone-treated children as illustrated in Table 7 Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial Follow-up Period

46 (3.4%) 16 (1.8%) 1 year‡ p = 0.025Non-Fluoroquinolone: ceftriaxone, amoxicillin/clavulanate, clarithromycin 2-sided Fisher's Exact Test 2-slued rished SCACL lest.

There were 1,199 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

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

→ 750 mg Tablet p.c.

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 torsades 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

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

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

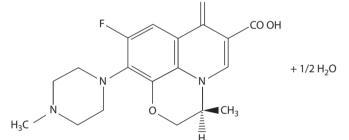
ealthcare provider if any symptoms of tendinitis or tendon rupture occur [see Boxed Warning; Warnings and Precautions (5.1); and Adverse

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 evofloxacin are not required following hemodialysis or CAPD [see Dosage and Administration (2.3)]. Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment

In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of

1,500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents. evofloxacin in 5% dextrose injection is a synthetic broad-spectrum antibacterial agent for intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyguinolone, 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 hemihydrat Figure 1: The Chemical Structure of Levofloxacin



M.W. 370.38 C<sub>18</sub>H<sub>20</sub>FN<sub>2</sub>O<sub>4</sub> • ½ H<sub>2</sub>O 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

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin 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 has the potential to form stable coordination compounds with many metal ions. This in vitro chelation potential has the following formation order: Al<sup>-2</sup>>Cu<sup>-2</sup>>Zn<sup>-2</sup>>Mg<sup>-2</sup>>Ca<sup>-2</sup>. Excipients and Description of Dosage Forms
The appearance of levofloxacin in 5% dextrose injection may range from a clear yellow to a clear greenish-yellow solution. This does not adversely affect product potency.

Levofloxacin Injection Premix in Single-Use Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging Terrorio As to 5.8. This is a dilute, non-pyrogenic, nearly isotonic premixed solution that contains levofloxacin in 5% Dextrose (D5W). Soll hydrochloric acid and sodium hydroxide may have been added to adjust the pH. The flexible container is fabricated from a specially formulated non-plasticized film containing polypropylene and thermoplastic elastomers The lieutoic containing polyproprieties in territoria specially intrinsiated in morphasticazed initin definition properties of the solution significantly. Solutions in contact with the flexible container can leach out certain of the container's chemical components in very small amounts within the expiration period. The suitability of the container material has been confirmed by tests in animals according to USP biological tests for plastic

Table 8: Mean ± SD Levofloxacin PK Parameters

12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action

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

-Thermean 🛨 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.

Regimen	C <sub>max</sub> (mcg/mL)	T <sub>max</sub> (h)	AUC (mcg•h/mL)	CL/F¹ (mL/min)	Vd/F² (L)	t <sub>1/2</sub> (h)	CL <sub>R</sub> (mL/min)
Single dose							
250 mg oral tablet <sup>3</sup>	$2.8 \pm 0.4$	1.6 ± 1	27.2 ± 3.9	156 ± 20	ND	$7.3 \pm 0.9$	142 ± 21
500 mg oral tablet3*	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	178 ± 28	ND	6.3 ± 0.6	103 ± 30
500 mg oral solution <sup>12</sup>	5.8 ± 1.8	$0.8 \pm 0.7$	47.8 ± 10.8	183 ± 40	112 ± 37.2	7 ± 1.4	ND
500 mg IV <sup>3</sup>	6.2 ± 1	1 ± 0.1	48.3 ± 5.4	175 ± 20	90 ± 11	6.4 ± 0.7	112 ± 25
750 mg oral tablet5*	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	129 ± 24	83 ± 17	7.5 ± 0.9	ND
750 mg IV <sup>5</sup>	11.5 ± 44	ND	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	ND
Multiple dose							
500 mg every 24h oral tablet <sup>3</sup>	5.7 ± 1.4	1.1 ± 0.4	47.5 ± 6.7	175 ± 25	102 ± 22	7.6 ± 1.6	116 ± 31
500 mg every 24h IV <sup>3</sup>	$6.4 \pm 0.8$	ND	54.6 ± 11.1	158 ± 29	91 ± 12	7 ± 0.8	99 ± 28
500 mg or 250 mg every 24h IV, patients with bacterial infection <sup>6</sup>	8.7 ± 4 <sup>7</sup>	ND	72.5 ± 51.2 <sup>7</sup>	154 ± 72	111 ± 58	ND	ND
750 mg every 24h oral tablet <sup>5</sup>	8.6 ± 1.9	1.4 ± 0.5	90.7 ± 17.6	143 ± 29	100 ± 16	8.8 ± 1.5	116 ± 28
750 mg every 24h IV5	12.1 ± 4.14	ND	108 ± 34	126 ± 37	80 ± 27	7.9 ± 1.9	ND
500 mg oral tablet sing	le dose, effects	of gender and a	ge:				,
Male <sup>8</sup>	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38
Female <sup>9</sup>	7 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40
Young <sup>10</sup>	5.5 ± 1	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6 ± 0.9	140 ± 33
Elderly <sup>11</sup>	7 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2	91 ± 29
500 mg oral single dos	e tablet, patients	with renal insu	fficiency:			•	•
CLCR 50 to 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 to 49 mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	51 ± 19	ND	27 ± 10	26 ± 13
CLCR < 20 mL/min	8.2 ± 2.6	1.1 ± 1	263.5 ± 72.5	33 ± 8	ND	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1	2.8 ± 2.2	ND	ND	ND	76 ± 42	ND

clearance/bioavailability

volume of distribution/bioavailability Healthy males 18 to 53 years of age 60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

healthy male and female subjects 18 to 54 years of age 500 mg every 48h for patients with moderate renal impairment (CLCR 20 to 50 mL/min) and infections of the respiratory tract or skin dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling healthy males 22 to 75 years of age healthy females 18 to 80 years of age

young healthy male and female subjects 18 to 36 years of age healthy elderly male and female subjects 66 to 80 years of age healthy males and females 19 to 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

ND=not determined 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 approximately 99%, certoinstating complete out assorption in evolutional in. Following a single intraventure does not evolution of the violation of the mean  $\pm$  SD peak plasma concentration attained was 6.2  $\pm$  1 mcg/mL after a 500 mg dose infused over 60 minutes and 11.5  $\pm$  4 mcg/mL after a 750 mg dose infused over 90 minutes. Levofloxacin Oral Solution and Tablet formulations are bioequivalent.

Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral or IV dosing regimens. Steady-state conditions are reached this index of the second seco 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 with food prolongs the time to peak concentration by approximately 1 hour and decreases the peak concentration by approximately 14% following tablet and approximately 25% following oral solution administration. Therefore, Levofloxacin Tablets can be administered without regard to food. It is recommended that Levofloxacin Oral Solution be

taken 1 hour before or 2 hours after eating. The plasma concentration profile of levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable (see Figure 2 and Figure 3).

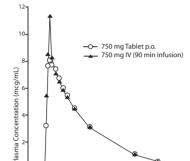


Figure 3: Mean Levofloxacin Plasma Concentration vs. Time Profile: 500 mg -O- 500 mg Tablet p.o.

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

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. 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. 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, expectively, indicating that secretion of levofloxacin cocurs in the renal proximal tubule. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine

clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy elderly subjects (66 to 80 years of age), the mean terminal plasma elimination half-life of levofloxacin was about 7.6 hours, as compared to approximately 6 hours in younger adults. The difference was attributable to the variation in renal function status of the subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by age. Levofloxacin dose adjustment based on age alone is not necessary [see Use in Specific Populations (8.5)].

The pharmacokinetics of levofloxacin following a single 7 mg/kg intravenous dose were investigated in pediatric patients ranging in age from 6 months to 16 years. Pediatric patients cleared levofloxacin faster than adult patients, resulting in lower plasma exposures than adults for a given mg/kg dose. Subsequent pharmacokinetic analyses predicted that a dosage regimen of 8 mg/kg every 12 hours (not to exceed 250 mg per dose) for pediatric patients 6 months to 17 years of age would achieve comparable steady-state plasma exposures (AUC , 24 and C , 24 and C , 27 to those observed in adult patients 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.

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

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 equired following hemodialysis or CAPD [see Dosage and Administration (2.3) and Use in Specific Populations (8.6)].

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),

The pharmacokinetics of levofloxacin in patients with serious community-acquired bacterial infections are comparable to those observed in healthy The potential for pharmacokinetic drug interactions between levofloxacin and antacids, warfarin, theophylline, cyclosporine, digoxin, probenecid, and cimetidine has been evaluated [see Drug Interactions (7)].

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 topoisor gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

Mechanism of Resistance uoroquinolone 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 β-lactam antibiotics, including penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10 to 10 levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoro

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

Gram-Positive Bacteria Staphylococcus aureus (methicillin-susceptible isolates) Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug-resistant isolates [MDRSP1]) MDRSP (Multi-drug-resistant Streptococcus pneumoniae) isolates are isolates resistant to two or more of the following antibiotics: penicillin (MIC ≥ 2 mcg/mL), 2nd generation cephalosporins, e.g., cefuroxime; macrolides, tetracyclines and trimethor

Gram-Negative Bacteria Escherichia coli Haemophilus influenzae nophilus parainfluenzae Legionella pneumophila Moraxella catarrhalis Proteus mirabilis Serratia marcescens

Other Bacteria Chlamydophila pneumonia Mycoplasma pneumoniae

The following in vitro data are available, but their clinical significance is unknown; Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC

Gram-Positive Bacteria β-hemolytic Streptococcus (Group G) Streptococcus agalactiae Viridans group streptococc Bacillus anthracis

Gram-Negative Bacteria Acinetobacter bauma Acinetobacter Iwoffii Bordetella pertussis Citrobacter koseri Citrobacter freundii Enterobacter sakazakii Klebsiella oxytoca Morganella morganii

antoea agglomerans Proteus vulgaris Providencia rettgeri Providencia stuartii Yersinia pestis Anaerobic Gram-Positive Bacteria

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.

Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method <sup>1,2,4</sup> (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder The MIC values should be interpreted according to the criteria outlined in Table 9. Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial

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

Table 9: Susceptibility Test Interpretive Criteria for Levofloxacin

		Minimum Inhibitory Concentrations (mcg/mL)				Disk Diffusion (zone diameter in mm)		
Pathogen	S	I	R	S	I	R		
Enterobacteriaceae	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Enterococcus faecalis	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Staphylococcus species	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Pseudomonas aeruginosa	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Haemophilus influenzae	≤2	†	-	≥ 17	-			
Haemophilus parainfluenzae	≤2			≥ 17				
Streptococcus pneumoniae	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Streptococcus pyogenes	≤2	4	≥8	≥ 17	14 to 16	≤ 13		
Yersinia pestis <sup>4</sup>	≤ 0.25							
Bacillus anthracis <sup>4</sup>	≤ 0.25							

S = Susceptible, I = Intermediate, R = Resistant The current absence of data on resistant isolates precludes defining any categories other than "Susceptible." Isolates yielding MIC/zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

A report of Susceptible indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations

Are point of susceptible indicates that the partogen is likely to be infinited in the antimicrobial compound in the 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. Standardized susceptibility test procedures require the use of laboratory controls to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test.<sup>1,2,3,4</sup> Standard levofloxacin powder should provide the range of

0.5 to 2

20 to 25

MIC values noted in Table 10. For the diffusion technique using the 5 mcg disk, the criteria in Table 10 should be achieved.

Table 10: Quality Control Ranges for Susceptibility Testing						
Microorganism	Microorganism QC Number	MIC (mcg/mL)	Disk Diffusion (zone diameter in mm)			
Enterococcus faecalis	ATCC 29212	0.25 to 2				
Escherichia coli	ATCC 25922	0.008 to 0.06	29 to 37			
Escherichia coli	ATCC 35218	0.015 to 0.06				
Haemophilus influenzae	ATCC 49247	0.008 to 0.03	32 to 40			
Pseudomonas aeruginosa	ATCC 27853	0.5 to 4	19 to 26			
Staphylococcus aureus	ATCC 29213	0.06 to 0.5				
Staphylococcus aureus	ATCC 25923	-	25 to 30			

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin did not shorten the time to tumor development of UV-induced skin tumors in hairless albino (Skh-1) mice at any levofloxacin dose level and was therefore not photo-carcinogenic under conditions of this study. Dermal levofloxacin concentrations in the hairless mice ranged from 25 to 42 mcg/g at the highest levofloxacin dose level (300 mg/kg/day) used in the photo-carcinogenicity study. By comparison, dermal levofloxacin concentrations in human subjects receiving 750 mg of levofloxacin averaged approximately 11.8 mcg/g at  $C_{\text{max}}$ .

ATCC 49619

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHO/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the in vitro chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays. Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day, corresponding to 4.2 times the highest recommended human dose based upon relative body surface area and intravenous doses as high as 100 mg/kg/day, corresponding to 1.2 times

the highest recommended human dose based upon relative body surface area. 13.2 Animal Toxicology and/or Pharmacology evofloxacin 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 to 5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats. Three-month old beagle dogs dosed orally with levofloxacin at 40 mg/kg/day exhibited clinically severe arthrotoxicity resulting in the termination of dosing at Day 8 of a 14-day dosing routine. Slight musculoskeletal clinical effects, in the absence of gross pathological or histopathological effects, resulted from the lowest dose level of 2.5 mg/kg/day (approximately 0.2-fold the pediatric dose based upon AUC comparisons). Synovitis and articular cartilage lesions were observed at the 10 and 40 mg/kg dose levels (approximately 0.7-fold and 2.4-fold the pediatric dose, respectively, based on AUC comparisons). Articular cartilage gross pathology and histopathology persisted to the end of the 18-week recovery period for those dogs from the 10 and 40 mg/kg/day dose levels When tested in a mouse ear swelling bioassay, levofloxacin exhibited phototoxicity similar in magnitude to ofloxacin, but less phototoxicity than other

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

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

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer nor inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated. 14 CLINICAL STUDIES

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multi-center, randomized, open-label study comparing intravenous leverlloxacin (750 mg once daily) followed by oral levofloxacin (750 mg once daily) for a total of 7 to 15 days to intravenous imipenem/cilastatin (500 to 1,000 mg every 6 to 8 hours daily) followed by oral levofloxacin (750 mg once daily) for a total of 7 to 15 days to intravenous imipenem/cilastatin (500 to 1,000 mg every 6 to 8 hours daily) followed by oral levofloxacin (750 mg once daily) for a total of 7 to 15 days to intravenous therapy (range: 1 to 16 days); comparator-treated patients received an average of 7 days of intravenous therapy (range: 1 to 16 days); comparator-treated patients received an average of 8 days of intravenous therapy (range: 1 to 19 days).

Overall, in the clinically and microbiologically evaluable population, adjunctive therapy was empirically initiated at study entry in 56 of 93 (60.2%) patients in the levofloxacin arm and 53 of 94 (56.4%) patients in the comparator arm. The average duration of adjunctive therapy was 7 days in the levofloxacin arm and 7 days in the comparator. In clinically and microbiologically evaluable patients with documented Pseudomonas aeruginosa infection, 15 of 17 (88.2%) received ceftazidime (N=11) or piperacillin/tazobactam (N=4) in the levofloxacin arm and 16 of 17 (94.1%) received an aminoglycoside in the comparator arm. Overall, in clinically and microbiologically evaluable patients, vancomycin was added to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin-resistant *S. aureus* infection. Clinical success rates in clinically and microbiologically evaluable patients at the post-therapy visit (primary study endpoint assessed on day 3 to 15 after completing therapy) were 58.1% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates at the post-therapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates at the post-therapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and bacteriological eradication rates by

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

Pathogen	N	Levofloxacin No. (%) of Patients Microbiologic/ Clinical Outcomes	N	Imipenem/Cilastatin No. (%) of Patients Microbiologic/ Clinical Outcomes
MSSA*	21	14 (66.7)/13 (61.9)	19	13 (68.4)/15 (78.9)
P. aeruginosa†	17	10 (58.8)/11 (64.7)	17	5 (29.4)/7 (41.2)
S. marcescens	11	9 (81.8)/7 (63.6)	7	2 (28.6)/3 (42.9)
E. coli	12	10 (83.3)/7 (58.3)	11	7 (63.6)/8 (72.7)
K. pneumoniae‡	11	9 (81.8)/5 (45.5)	7	6 (85.7)/3 (42.9)
H. influenzae	16	13 (81.3)/10 (62.5)	15	14 (93.3)/11 (73.3)
S. pneumoniae	4	3 (75)/3 (75)	7	5 (71.4)/4 (57.1)

interticulin resusception 6. aureus
See above text for use of combination therapy
The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study 14.2 Community-Acquired Pneumonia: 7 to 14 day Treatment Regimen

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in 2 pivotal clinical studies. In the first study, 590 patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days. Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days post-therapy, and 3 to 4 weeks post-therapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days post-therapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). The 95% CI for the difference of response rates (levofloxacin minus comparator) was I-6, 191. In the second study, 264 patients were enrolled in a prospective, multi-center, nonto response rates (evolutional minus comparation) was [-0, 19]. In the second study, zer parameter with a prospective, multi-denier, 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. Bacteriologic eradication rates across both studies are presented in Table 12. Table 12: Bacteriological Eradication Rates Across 2 Community-Acquired Pneumonia Clinical Studies

M. catarrhalis

evofloxacin was effective for the treatment of community-acquired pneumonia caused by multi-drug-resistant Streptococcus pneumoniae (MDRSP)

MDRSP isolates are isolates resistant to two or more of the following antibacterials; penicillin (MIC  $\geq$  2 mcg/mL), 2<sup>nd</sup> generation cephalosporins (e.g. refuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole). Of 40 microbiologically evaluable patients with MDRSP isolates, 38 patient

(95%) achieved clinical and bacteriologic success at post-therapy. The clinical and bacterial success rates are shown in Table 13. Table 13: Clinical and Bacterial Success Rates for Levofloxacin-Treated MDRSP in

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

Screening Susceptibility	Clinical S	uccess	Bacteriological Success*	
	n/N <sup>†</sup>	%	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

on respiratory isolate. n = the number of microbiologically evaluable patients who were clinical successes; N = number of microbiologically evaluable patients in thedesignated resistance group.

n = the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N = number of MDRSP isolates in a 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 Success Eradication esistant to 2 antibacterials 17/18 (94.4%) 17/18 (94.4%) 14/15 (93.3%) 14/15 (93.3%) istant to 3 antibacterials 7/7 (100%) Resistant to 4 antibacterials 7/7 (100%) 8/9 (89%) 8/9 (89%) 14.3 Community-Acquired Pneumonia: 5-day Treatment Regimen
To evaluate the safety and efficacy of the higher dose and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically an

adiologically determined mild to severe community-acquired pneumonia were evaluated in a double-blind, randomized, prospective, multi-center study comparing levofloxacin 750 mg, IV or orally, every day for five days or levofloxacin 500 mg, IV or orally, every day for 10 days.

Clinical success rates (cure plus improvement) in the clinically evaluable population were 90.9% in the levofloxacin 750 mg group and 91.1% in the levofloxacin 500 mg group. The 95% CI for the difference of response rates (levofloxacin 750 minus levofloxacin 500) was [-5.9, 5.4]. In the clinically evaluable population (31 to 38 days after enrollment) pneumonia was observed in 7 out of 151 patients in the levofloxacin 750 mg group and 2 out of 147 patients in the levofloxacin 500 mg group. Given the small numbers observed, the significance of this finding cannot be determined statistically. he microbiological efficacy of the 5-day regimen was documented for infections listed in Table 1

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

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

14.4 Acute Bacterial Sinusitis: 5-day and 10 to 14 day Treatment Regimens .evofloxacin is approved for the treatment of acute bacterial sinusitis (ABS) using either 750 mg by mouth x 5 days or 500 mg by mouth once daily x 10 to 14 days. To evaluate the safety and efficacy of a high dose short course of levofloxacin, 780 outpatient adults with clinically and radiologically determined acute bacterial sinusitis were evaluated in a double-blind, randomized, prospective, multi-center study comparing levofloxacin 750 mg by mouth once daily for five days to levofloxacin 500 mg by mouth once daily for 10 days. Clinical success rates (defined as complete or partial resolution of the pre-treatment signs and symptoms of ABS to such an extent that no further antibiotic treatment was deemed necessary) in the microbiologically evaluable population were 91.4% (139/152) in the levofloxacin 750 mg group and 88.6% (132/149) in the levofloxacin 500 mg group at the test-of-cure (TOC) visit (95% CI [-4.2, 10] for levofloxacin 750 mg minus levofloxacin 500 mg).

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

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

26/27 (96.3%)
25/27 (92.6%)
13/13 (100%)
p

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 to 5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator. Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs. 14.6 Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB<sub>3</sub>) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multi-center, 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 emploint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5 to 18 days after completion of therapy was 75% in the levofloxacin group and 76.8% in the ciprofloxacin group (95% CI [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented in Table 17

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

	Levofloxacin (N=136)		Ciprofloxacin (N=125)		
Pathogen	N	Eradication	N	Eradication	
E. coli	15	14 (93.3%)	11	9 (81.8%)	
E. faecalis	54	39 (72.2%)	44	33 (75%)	
S. epidermidis*	11	9 (81.8%)	14	11 (78.6%)	
* Eradication rates shown are for patients who had a sole pathogen only; mixed cultures were excluded.					

completion of therapy were 75% for levofloxacin-treated patients and 72.8% for ciprofloxacin-treated patients (95% CI [-8.87, 13.27] for levofloxacin minus ciprofloxacin). Clinical long-term success (24 to 45 days after completion of therapy) rates were 66.7% for the levofloxacin-treated patients and 76.9% for the ciprofloxacin-treated patients (95% CI [-23.4, 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, 1,109 patients with cUTI and AP were enrolled in a randomized, double-blind, multi-center clinical trial conducted in the US from November 2004 to April 2006 comparing levofloxacin 750 mg IV or orally once daily for 5 days (565 patients) with AP complicated

Clinical success (cure + improvement with no need for further antibiotic therapy) rates in microbiologically evaluable population 5 to 18 days after

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

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

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

	Levoflo		Ciprofloxacin 400 mg IV/500 mg orally twice daily for 10 days		Overall Difference [95% CI]	
	750 mg orally or IV or	nce daily for 5 days				
	n/N	%	n/N	%	Levofloxacin-Ciprofloxaci	
		ml	TT Population*			
Overall (cUTI or AP)	252/333	75.7	239/318	75.2	0.5 (-6.1, 7.1)	
cUTI	168/230	73	157/213	73.7		
AP	84/103	81.6	82/105	78.1		
		Microbiologica	ally Evaluable Population†			
Overall (cUTI or AP)	228/265	86	215/241	89.2	-3.2 [-8.9, 2.5]	
cUTI	154/185	83.2	144/165	87.3		
AP	74/80	92.5	71/76	93.4		

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 ≥ 10<sup>5</sup> CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to Bacteriologic 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

Bacteriological Eradication Rate

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 Regime To evaluate the safety and efficacy of the 250 mg dose, 10 day regimen of levofloxacin, 567 patients with uncomplicated UTI, mild-to-moderate cUTI, and mild-to-moderate AP were enrolled in a randomized, double-blind, multi-center clinical trial conducted in the US from June 1993 to January 1995 comparing levofloxacin 250 mg orally once daily for 10 days (285 patients) with ciprofloxacin 500 mg orally twice daily for 10 days (282 patients). Patients with a resistant pathogen, recurrent UTI, women over age 55 years, and with an indwelling catheter were initially excluded, prior to protocol 1 to 12 days post-therapy in patients with a pathogen identified at baseline

The bacteriologic cure rates overall for levofloxacin and control at the test-of-cure (TOC) visit for the group of all patients with a documented pathogen

eline (modified intent to treat ble) are summarized in Table	or mITT) and the group of patier e 20.	nts in the mITT population who	closely followed the protocol (I	Microbiologicall
	Table 20: Bacteriological Era	adication Overall (cUTI or AP)	at Test-Of-Cure*	
	Levofloxacin 250 mg once daily for 10 days		Ciproflox: 500 mg twice daily	
	n/N	%	n/N	%
Population <sup>†</sup>	174/209	83.3	184/219	84
biologically Evaluable	164/177	92.7	159/171	93

1 to 9 days post-therapy for 30% of subjects enrolled prior to a protocol amendment; 5 to 12 days post-therapy for 70% of subjects. The mITT population included patients who had a pathogen isolated at baseline. Patients with missing res counted as failures in this 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 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  $5.7 \pm 1.4$  and  $6.4 \pm 0.8$  mcg/mL, respectively; and the corresponding total plasma exposure (AUC<sub>0.32</sub>) is  $47.5 \pm 6.7$  and  $54.6 \pm 11.1$  mcg·h/mL, respectively. The predicted steady-state pharmacokinetic parameters in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally every 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)]. In adults, the safety of levofloxacin for treatment durations of up to 28 days is well characterized. However, information pertaining to extended use at In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of

musculoskeletal adverse events (arthralgia, arthritis, tendinopathy, gait abnormality) compared to controls has been observed in clinical studies with treatment duration of up to 14 days. Long-term safety data, including effects on cartilage, following the administration of levofloxacin to pediatric patients is limited [see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)]. A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 49 LD., (~2.7 X 106) spores (range 17 to 118 LD.,) of B. anthracis (Ames strain) was conducted. The minimal inhibitory concentration (MIC) of levofloxacin for the anthrax strain used in this study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T<sub>max</sub> (1 hour post-dose) following oral dosing to steady-state ranged from 2.79 to 4.87 mcg/mL. Steady-state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL.

Mean (SD) steady-state AUC $_{0.24}$  was 33.4  $\pm$  3.2 mcg+h/mL (range 30.4 to 36 mcg+h/mL). Mortality due to anthrax for animals that received a 30.4 to 36 mcg+h/mL). lay regimen of oral levofloxacin beginning 24 hrs post-exposure was significantly lower (1/10), compared to the placebo group (9/10) [P=0.001 2-sided Fisher's Exact Test]. The one levofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period. fficacy studies of levofloxacin could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval

The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in an African greer monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [see Indications and Usage (1.14) and Dosage and Administration (2.1, 2.2)]. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean  $(\pm SD)$  steady-state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is  $5.7 \pm 1.4$  and  $6.4 \pm 0.8$  mcg/mL, respectively; and the corresponding total plasma exposure  $(AUC_{g_2g})$  is  $47.5 \pm 6.7$  and  $54.6 \pm 11.1$  mcg·h/mL, respectively. The predicted steady-state pharmacokinetic parameters

of this indication was based on an efficacy study conducted in animals.

alculated to be comparable to those observed in adults receiving 500 mg orally once daily [see Clinical Pharmacology (12.3)]. 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 3.5 mcg/mL in African green monkeys. Trough concentrations at 24 hours post-dose ranged from < 0.03 to 0.06 mog/mL. Mean (SD) AUC, was 11.9 (3.1) mcg-h/mL (range 9.5 to 16.86 mcg-h/mL). Animals were randomized to receive either a 10-day regimen of IV levofloxacin or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39°C for more than 1 hour). Mortality in the levofloxacin group was significantly lower 1/17) compared to the placebo group (7/7) [p<0.001, Fisher's Exact Test; exact 95% confidence interval (-99.9%, -55.5%) for the difference

n 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

Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Approved Standard-9" ed. CLSI Document M7-A9, CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA, 2012.

CLSI. Performance Standards for Antimicrobial Susceptibility Testing; 22" Informational Supplement. CLSI Document M100-S22, 2012.

CLSI. Performance Standards for Antimicrobial Disk Susceptibility Testing; 22" Informational Supplement. CLSI M2-A11, 2012.

CLSI. Methods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline-2<sup>nd</sup> ed. CLSI Document M45-A2, 2010.

16.1 Levofloxacin Injection Pre-Mixed Solution, Single-Use in Flexible Container
Levofloxacin in 5% Dextrose Injection is supplied as a single-use, premixed solution in flexible containers. Each bag contains a dilute solution with the equivalent of 250, 500, or 750 mg of levofloxacin, respectively, in 5% Dextrose (D5W).

63323-355-50 250 mg, in flexible container, 50 mL fill. 5 mg per mL 500 mg, in flexible container, 100 mL fill. 63323-355-65 5 mg per mL 750 mg, in flexible container, 150 mL fill. 63323-355-60 5 mg per mL Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Avoid excessive heat and protect from freezing and light.

The container closure is not made with natural rubber latex. Non-PVC, Non-DEHP, Sterile.

#### 17 PATIENT COUNSELING INFORMATION 17.1 Antibacterial Resistance

16 HOW SUPPLIED/STORAGE AND HANDLING

15 REFERENCES

cold). When levofloxacin is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by levofloxacin or other antibacterial drugs in the future. 17.2 Administration with Fluids nts should drink fluids liberally while taking levofloxacin to avoid formation of a highly concentrated urine and crystal formation in the urine. 17.3 Serious and Potentially Serious Adverse Reactions

Antibacterial drugs including levofloxacin should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common

Tendon Disorders: Patients should contact their healthcare provider if they experience pain, swelling, or inflammation of a tendon, or weakness or inability to use one of their joints; rest and refrain from exercise; and discontinue levofloxacin treatment. The risk of severe endon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Exacerbation of Myasthenia Gravis: Patients should inform their physician of any history of myasthenia gravis. Patients should notify their

physician if they experience any symptoms of muscle weakness, including respiratory difficulties Hypersensitivity Reactions: Patients should be informed that levofloxacin can cause hypersensitivity reactions, even following the first dose. Patients should discontinue the drug at the first sign of a skin rash, hives or other skin reactions, a rapid heartbeat, difficulty in swallowing or breathing, any swelling suggesting angioedema (e.g., swelling of the lips, tongue, face, tightness of the throat, hoarseness), or other symptoms

atients should be informed of the following serious adverse reactions that have been associated with levofloxacin or other fluoroquinolone use:

Hepatotoxicity: Severe hepatotoxicity (including acute hepatitis and fatal events) has been reported in patients taking levofloxacin. Patients should inform their physician and be instructed to discontinue levofloxacin treatment immediately if they experience any signs or symptoms of liver injury including: loss of appetite, nausea, vomiting, fever, weakness, tiredness, right upper quadrant tenderness, itching, yellowing of the skin and eyes, light colored bowel movements or dark colored urine. Convulsions: Convulsions have been reported in patients taking fluoroquinolones, including levofloxacin. Patients should notify their physician before taking this drug if they have a history of convulsions

Neurologic Adverse Effects (e.g., dizziness, lightheadedness, increased intracranial pressure): Patients should know how they react to levofloxacin before they operate an automobile or machinery or engage in other activities requiring mental alertness and coordination. Patients should notify their physician if persistent headache with or without blurred vision occurs. Diarrhea: Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

Peripheral Neuropathies: Patients should be informed that peripheral neuropathy has been associated with levofloxacin use. Symptoms may occur soon after initiation of therapy and may be irreversible. If symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop, patients should immediately discontinue treatment and contact their physician. Prolongation of the QT Interval: Patients should inform their physician of any personal or family history of QT prolongation or proarrhythmic conditions such as hypokalemia, bradycardia, or recent myocardial ischemia; if they are taking any Class IA (quinidine, procainamide), or Class III (amiodarone, sotalol) anti-arrhythmic agents. Patients should notify their physicians if they have any symptoms of prolongation of the QT interval, including prolonged heart palpitations or a loss of consciousness.

problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any tendon or joint-related problems that occur during or following levofloxacin therapy [see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)]. Photosensitivity/Phototoxicity: Patients should be advised that photosensitivity/phototoxicity has been reported in patients receiving fluoroquinolone antibiotics. Patients should minimize or avoid exposure to natural or artificial sunlight (tanning beds or UVA/B treatment) while taking fluoroquinolones. If patients need to be outdoors when taking fluoroquinolones, they should wear loose-fitting clothes that protect skin om sun exposure and discuss other sun protection measures with their physician. If a sunburn-like reaction or skin eruption occurs, patients

17.4 Drug Interactions with Insulin, Oral Hypoglycemic Agents, and Warfarin
Patients should be informed that if they are diabetic and are being treated with insulin or an oral hypoglycemic agent and a hypoglycemic reaction occurs, they should discontinue levofloxacin and consult a physician.

Patients should be informed that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin, be nonitored for evidence of bleeding, and also have their anticoagulation tests closely monitored while taking warfarin co Patients given levofloxacin for these conditions should be informed that efficacy studies could not be conducted in humans for ethical and feasibility reasons. Therefore, approval for these conditions was based on efficacy studies conducted in animals

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