Image: Non-static region Strength Dosed Every 24 hours Duration (days) ⁺ LEVOFLOXACIN IN 5% DEXTROSE INJECTION, Solution for Intravenous Use Initial U.S. Approval: 1996 Strength Strength Duration (days) ⁺ 5.6 Central Nervous System Effects Community-Acquired Pneumonia [±] 500 mg in 100 mL 500 mg in 100 mL Storegion in 50 mg 7 to 14 Storegion in 50 mg in 150 mL Storegion in 50 mg 5.0 community-Acquired Pneumonia [±] 5.0 mg in 150 mL Storegion in 50 mg 5.0 mg in 150 mL Storegion in 50 mg 5.0 mg in 150 mL Storegion in 50 mg 5.0 mg in 150 mL Storegion in 50 mg Storegion in 50 mg Storegion in 16 mervous System Effects Storegion in 16 mervous System Ef	HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not information needed to use LEVOFLOXACIN IN 5% DEXTROSE INJECTION safely and effectively. See full prescribing information for LEVOFLOXACIN IN 5% DEXTROSE INJECTION. These highlights do not information for LEVOFLOXACIN IN 5% DEXTROSE INJECTION safely and effectively. See full prescribing information for LEVOFLOXACIN IN 5% DEXTROSE INJECTION.	 Tan et la dira in a factoria que na da vacion que a presentan de la vacion que a conserver de deputiences en entre de expensiones en expensiones en entre de expensiones en expensiones en entre de expensiones en entre de expensiones entre de expensiones en entre de expensiones en entre de expensiones en
s system stimulation which may lead to tremors, restlessness, omnia, and, rarely, suicidal thoughts or acts. These reactions		th rheumatoid arthritis (RA) sign of tendon pain, swelling or inflammation. Stop taking Levofloxacin until tendinitis or tendon rupture has been ruled out by the affected area. Achilles tendon at the back of your ankle. This can also happen with other tendons. Talk to your healthcare provider about the xacin. You may need a different antibiotic that is not a fluoroquinolone to treat your infection. after you have finished taking Levofloxacin. Tendon ruptures have happened up to several months after people have finished
always possible. Table 6: Post-marketing Reports of Adverse Drug Reactions	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	17.6 FDA-Approved Medication Guide Frequencies Figure F

WARNING: See full prescribing information for complete boxed warning. Iuoroquinolones, including Levofloxacin in 5% Dextrose 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 cortice 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)]

o 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 bacteria.

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 s (5.7) cur in order to prevent irreversibility (5.8) have been reported. Avoid use in patients with known prolongation, those

Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses (5.4)

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

---CONTRAINDICATIONS-

---WARNINGS AND PRECAUTIONS--

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)

Type of Infection*	Dosed Every 24 hours	Duration (days)
Nosocomial Pneumonia	750 mg	7 to 14
Community-Acquired Pneumonia [‡]	500 mg	7 to 14
Community-Acquired Pneumonia [§]	750 mg	5
Acute Bacterial Sinusitis	750 mg	5
	500 mg	10 to 14
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	7
Complicated Skin and Skin Structure Infections (SSSI)	750 mg	7 to 14
Uncomplicated SSSI	500 mg	7 to 10
Chronic Bacterial Prostatitis	500 mg	28
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP) [§]	750 mg	5
Complicated Urinary Tract Infection (cUTI) or Acute Pyelonephritis (AP)#	250 mg	10
Uncomplicated Urinary Tract Infection	250 mg	3
Inhalational Anthrax (Post-Exposure), adult and pediatric patients > 50 kg ^{b,6}	500 mg	60 ⁶
Pediatric patients < 50 kg and \geq 6 months of age ^{b,6}	see Table 2 below (2.2)	60 ⁶
Plague, adult and pediatric patients > 50 kg ^a	500 mg	10 to 14
Pediatric patients < 50 kg and \geq 6 months of age	See Table 2 below (2.2)	10 to 14

Sequential interapy (intraventos to ran may be instituted at the discretion of the physician. Due to methicillin-susceptible Staphylococcus aureus, Streptococcus preumoniae (including multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae, Legionella pneumophila, or

Due to Streptococcus pneumoniae (excluding multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae,

Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Indications and Usage (1.3)]. This regimen is indicated for cUTI due to Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis and AP due to E. coli, including cases with

This regimen is indicated for cUTI due to Enterococcus faecalis, Enterococcus cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,

Pseudomona serviginos: 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

Drug administration should begin as soon as possible after suspected or confirmed exposure to Yersinia pestis. Higher doses of levofloxacin

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

Dose

500 mg

Freq. Once Every

24 hr

Duration[†]

60 days§

typically used for treatment of pneumonia can be used for treatment of plague, if clinically indicated

The dosage in pediatric patients \geq 6 months of age is described below in Table 2.

studied. An increased in indexion of unavoidskieletal 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

* Due to the designated pathogens [see Indications and Usage (1)]. equential therapy (intravenous to oral) may be instituted at the discretion of the physician.

Mycoplasma pneumoniae [see Indications and Usage (1.2)].

ncurrent bacteremia.

benefit outweighs the risk.

2.2 Dosage in Pediatric Patients

lational Anthrax (post-exposure)

Studies (14.9)].

Type of Infection*

Pediatric patients > 50 kg

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 fluoroguinolones, levofloxacin social in patients receiving evoluciant in a province and appropriate measures instituted. As with other fluoroguinolones, 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., certain drug therapy, renal dysfunction) (see Adverse Reactions factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction) (see Adverse Reactions (6), Drug Interactions (7.4, 7.5) 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)].

System/Organ Class	Adverse Reaction
Blood and Lymphatic System Disorders mmune System Disorders	pancytopenia aplastic anemia leukopenia hemolytic anemia <i>[see Warnings and Precautions (5.4)]</i> eosinophilia hypersensitivity reactions, sometimes fatal including:
	anaphylactic/anaphylactoid reactions anaphylactic shock angioneurotic edema serum sickness [see Warnings and Precautions (5.3, 5.4)]
Psychiatric Disorders	psychosis paranoia isolated reports of suicide attempt and suicidal ideation [see Warnings and Precautions (5.6)]
Nervous System Disorders	exacerbation of myasthenia gravis [see Warnings and Precautions (5.2)] anosmia ageusia parosmia dysgeusia peripheral neuropathy (may be irreversible) [see Warnings and Precautions (5.8)] isolated reports of encephalopathy abnormal electroencephalogram (EEG) dysphonia pseudotumor cerebri [see Warnings and Precautions (5.6)]
Eye Disorders	uveitis vision disturbance, including diplopia visual acuity reduced vision blurred scotoma
Ear and Labyrinth Disorders	hypoacusis tinnitus
Cardiac Disorders	isolated reports of torsades de pointes electrocardiogram OT prolonged [see Warnings and Precautions (5.9)] tachvcardia
/ascular Disorders	vasodilatation
Respiratory, Thoracic and Mediastinal Disorders	isolated reports of allergic pneumonitis [see Warnings and Precautions (5.4)]
Hepatobiliary Disorders	hepatic failure (including fatal cases) hepatitis jaundice [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)] leukocytoclastic vasculitis
Musculoskeletal and Connective Tissue Disorders	tendon rupture <i>[see Warnings and Precautions (5.1)]</i> muscle injury, including rupture rhabdomyolysis
Renal and Urinary Disorders	interstitial nephritis [see Warnings and Precautions (5.4)]
Seneral Disorders and Administration Site Conditions	multi-organ failure pyrexia
nvestigations	prothrombin time prolonged international normalized ratio prolonged muscle enzymes increased

INDICATIONS AND USAGE- evofloxacin in 5% Dextrose Injection is a fluoroquinolone antibacterial indicated in adul esignated, susceptible bacteria (1, 12.4). Pneumonia: nosocomial (1.1) and community-acquired (1.2, 1.3) Acute bacterial isinusitis (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) Urinary 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 ADMINISTRATI	ts (≥ 18 years of age) with infections cau	sed by	Central nervous system effects, in in patients with known or suspect (pseudotumor cerebri) has been n <i>Clostridium difficile</i> -associated col Peripheral neuropathy: discontinu Prolongation of the QT interval an with hypokalemia, and with other of The most common reactions (≥ 3%) w	tits: evaluate if diarrhea occurs (5.7) e immediately if symptoms occur in order to prevent irreversibility (5.8) d isolated cases of torsades de pointes have been reported. Avoid use in pa drugs that prolong the QT interval (5.9, 8.5) ADVERSE REACTIONS	ur after the first dose. Use with caution shold. Increased intracranial pressure attents with known prolongation, those
Dosage in patients with normal renal function (2.1)				DRUG INTERACTIONS	
Type of Infection	Dose Every	Duration	Interacting Drug	Interaction	
	24 hours	(days)	Multivalent cation-containing products including antacids,	Absorption of levofloxacin is decreased when the tablet or oral solution of these products. Do not co-administer the intravenous formulation in	
Nosocomial Pneumonia (1.1) Community-Acquired Pneumonia (1.2)	750 mg 500 mg	7 to 14 7 to 14	metal cations or didanosine Warfarin	cation, e.g., magnesium (2.4, 7.1) Effect may be enhanced. Monitor prothrombin time, INR, watch for blee	ding (7.2)
Community-Acquired Pneumonia (1.3)	750 mg	5	Anti-diabetic agents	Carefully monitor blood glucose (5.11, 7.3)	
Acute Bacterial Sinusitis (1.4)	750 mg 500 mg	5 10 to 14			
Acute Bacterial Exacerbation of Chronic Bronchitis (1.5)	500 mg	7		USE IN SPECIFIC POPULATIONS	
Complicated Skin and Skin Structure Infections (SSSI) (1.6)	750 mg	7 to 14		has been reported. The majority of reports describe patients 65 years of ag cluding rupture), especially with concomitant corticosteroid use (5.1, 8.5, 17)	
Uncomplicated SSSI (1.7) Chronic Bacterial Prostatitis (1.8)	500 mg 500 mg	7 to 10 28	prolongation of the QT interval (5.		,
Complicated Urinary Tract Infection (1.9) or Acute Pyelonephritis (1.11)	750 mg	5	comparator. Shown to cause arth	ropathy and osteochondrosis in juvenile animals (5.10, 8.4, 13.2). Safety in	pediatric patients treated for more
Complicated Urinary Tract Infection (1.10) or Acute Pyelonephritis (1.11) Uncomplicated Urinary Tract Infection (1.12)	250 mg 250 mg	10	than 14 days has not been studied plague (1.14, 2.2, 8.4, 14.10).	d. Risk-benefit appropriate only for the treatment of inhalational anthrax (po	st-exposure) (1.13, 2.2, 8.4, 14.9) and
Inhalational Anthrax (Post-Exposure) (1.13)					
Adults and Pediatric Patients > 50 kg	500 mg	60	See 17 for PATIENT COUNSELING I	NFORMATION and the FDA-approved Medication Guide.	
Pediatric Patients < 50 kg and ≥ 6 months of age	8 mg/kg BID (not to exceed 250 mg/dose)	60			Revised: March 2015
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			
ULL PRESCRIBING INFORMATION: CONTENTS* /ARNING: INDICATIONS AND USAGE 1.1 Nosocomial Pneumonia 1.2 Community-Acquired Pneumonia: 7 to 14 day Treatment Regimen			7.6 Cyclosporine 7.7 Digoxin 7.8 Probenecid and Cimetidine 7.9 Interactions with Laborator 8 USE IN SPECIFIC POPULATION 8.1 Pregnancy	v or Diagnostic Testing	01-59-12-002B
1.3 Community-Acquired Pneumonia: 5-day Treatment Regiment Acute Bacterial Sinusitis: 5-day and 10 to 14 day Treatment Regimens Acute Bacterial Exacerbation of Chronic Bronchitis Complicated Skin and Skin Structure Infections Uncomplicated Skin and Skin Structure Infections Chronic Bacterial Prostatitis -I.9 - Complicated Jinary Treat Infections: 5-day-Treatment-Regimen			8.3 Nursing Mothers 8.4 Pediatric Use 8.5 Geriatric Use 8.6 Renal Impairment 8.7 Hepatic Impairment 10 OVERDOSAGE 11_DESCRIPTION 12 CLINICAL PHARMACOLOGY		
 1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen 1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen 1.12 Uncomplicated Urinary Tract Infections 1.13 Inhalational Anthrax (Post-Exposure) 1.14 Plague DOSAGE AND ADMINISTRATION 2.1 Dosage in Adult Patients with Normal Renal Function 2.2 Dosage in Pediatric Patients 2.3 Dosage Adjustment in Adults with Renal Impairment 2.4 Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Cations, No. 2, Advance and Catalant Catalant, Statistical Advances 2.6 Administration Instructions 2.6 Preparation of Intravenous Product DOSAGE FORMS AND STRENGTHS CONTRAINDICATIONS WARNINGS AND PRECAUTIONS 5.1 Tendinopathy and Tendon Rupture 2.2 Exacerbation of Myasthenia Gravis 3.3 Hypersensitivity Reactions 5.4 Other Serious and Sometimes Fatal Reactions 5.5 Hepatoxicity 5.6 Central Nervous System Effects 7 Clostridium difficiparders 8 Peripheral Neuropathy 5.9 Prolongation of the QT Interval 5.1 Blood Glucose Disturbances 5.1 Photosensitivity/Phototoxicity 5.3 Development of Drug-Resistant Bacteria ADVERSE REACTIONS 6.1 Serious and Otherwise Important Adverse Reactions 5.2 Clinical Trial Experience 6.3 Post-marketing Experience 6.3 Post-marketing Experience 6.3 Post-marketing Experience 7.1 Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins 7.2 Warfarin 7.3 Anti-diabetic Agents 7.4 Non-Steroidal Anti-Inflammatory Drugs 7.5 Theophylline 			 12.1 Mechanism of Action 12.3 Pharmacokinetics 12.4 Microbiology 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagene 13.2 Animal Toxicology and/or P 14 CLINICAL STUDIES 14.1 Nosocomial Pneumonia 14.2 Community-Acquired Pneu 14.3 Complicated Vinay Tract 14.5 Complicated Vinary Tract 14.6 Chronic Bacterial Invisions 14.5 Complicated Uninary Tract 14.9 Inhalational Anthrax (Post-I 14.10 Plague 15 REFERENCES 16 HOW SUPPLIED/STORAGE AND 17.1 Antibacterial Resistance 17.2 Administration with Fluids 17.5 Plague and Anthrax Studie 17.6 FDA-Approved Medication 	harmacology monia: 7 to 14 day Treatment Regimen monia: 5-day Treatment Regimen day and 10 to 14 day Treatment Regimens Structure Infections and Acute Pyelonephritis: 5-day Treatment Regimen Infections and Acute Pyelonephritis: 10-day Treatment Regimen Exposure) D HANDLING Waxed Solution, Single-Use in Flexible Container IATION ious Adverse Reactions in, Oral Hypoglycemic Agents, and Warfarin s	
ULL PRESCRIBING INFORMATION WARNING: Fluoroquinolones, including Levofloxacin in 5% Dextrose Injection, are associa	ated with an increased risk of tendini	tis and tendon		icture Infections ient of complicated skin and skin structure infections due to methicillin-susc pyogenes, or Proteus mirabilis [see Clinical Studies (14.5)].	eptible Staphylococcus aureus,

upture 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 myastheni gravis. Avoid Levofloxacin in 5% Dextrose Injection in patients with a known history of myasthenia gravis [see Warnings and Demonstrate of 5.01] Precautions (5.2)].

1 INDICATIONS AND USAGE

dinopathy, and gait abnormality) seen in more levofloxacin-treated patients than in s in juvenile animals (5.10, 8.4, 13.2). Safety in pediatric patients treated for more nly for the treatment of inhalational anthrax (post-exposure) (1.13, 2.2, 8.4, 14.9) and Pediatric patients < 50 kg and \geq 6 months of age 60 days[§] 8 mg/kg (not to exceed 250 mg per dose) 12 hr Pediatric patients > 50 kg 500 mg 24 hr 10 to 14 days Revised: March 2015 8 mg/kg (not to exceed 250 mg per dose) Pediatric patients < 50 kg and \geq 6 months of age 12 hr 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 Administer levofloxacin with caution in the presence of renal insufficiency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. No adjustment is necessary for patients with a creatinine clearance ≥ 50 mL/min. In patients with impaired renal function (creatinine clearance < 50 mL/min), adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance [see Use in Specific Populations (8.6)]. Table 3 shows how to adjust dose based on creatinine clearance. Table 3: Dosage Adjustment in Adult Patients with Renal Impairment (creatinine clearance < 50 mL/min) Dosage in Normal Renal Function Every 24 hours Creatinine Clearance 20 to 49 mL/min Creatinine Clearance Hemodialysis or Chronic Ambulatory Peritoneal Dialysis 10 to 19 mL/min 01-59-12-002B (CAPD) 750 mg 50 mg every 48 hours 50 mg initial dose, then 500 mg 750 mg initial dose, then 500 mg every 48 hours every 48 hours 500 mg initial dose, then 250 mg 500 mg initial dose, then 250 mg 500 mg initial dose, then 250 mg every 24 hours 500 mg initial dose, then 250 mg every 48 hours 500 mg 250 mg No dosage adjustment required 250 mg every 48 hours. If treating uncomplicated UTI, then no is available is available dosage adjustment is required

2.4 Drug Interaction with Chelation Agents: Antacids, Sucralfate, Metal Cations, Multivitamins 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)].

2.5 Administration Instructions

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. Levoloxacia 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)].

2.6 Preparation of Intravenous Product

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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) definition of use the same after drugs in the same after infusion of levofloxacin in 5% dextrose injection and with any other drug(s) definition of use the same after drugs in the same after drugs and the same after drugs in the same after drugs and the sa administered via this common line.

Levofloxacin Injection Premix in Single-Use Flexible Containers (5 mg/mL) Levofloxacin in 5% dextrose 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 levofloxacin solution. The concentration of each container is 5 mg/mL. No further dilution of these preparations is necessary. Because the premix deviation and the content of the environment of the officer deviation of the second preparations is necessary. 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:

II Situations for the varia of the notes and remove solution container. 2. 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.
 Do not use if the solution is cloudy or a precipitate is present.
- Use sterile equipment.
- 5. WARNING: Do not admix with other drugs or additives. Such use could result in air embolism due to residual air being drawn from the primary container before administ tration of the fluid from the secondary container is comple

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.
- 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.

5 WARNINGS AND PRECAUTIONS

5.1 Tendinopathy and Tendon Rupture

5.2 Exacerbation of Myasthenia Gravis

seling Information (17.3)

5.3 Hypersensitivity Reactions

- 250 mg, in flexible container, 50 mL fill
- intraindicated in persons with known hypersensitivity to levofloxacin, or o (5.3)].

In renambury and remain repairs and the second repairs and the second rest of the second repairs and the second re

frequently involves the Achilles tendon, and runture of the Achilles tendon may require surgical renair. Tendinitis and tendon runture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroguinolone-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 races 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 tendinities 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)].

luoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with fluoroquinolones,

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)]

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

including levofloxacin. These reactions after out of the inter the second secon

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

5.8 Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including levofloxacin. Symptoms may occur soon after initiation of levofloxacin and may be irreversible. Levofloxacin should be discontinued immediately if the patient experiences symptoms of neuropathy including pain, burning, tingling, numberss, 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 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 nt Counseling Information (17.3)].

5.10 Musculoskeletal Disorders in Pediatric Patients and Arthropathic Effects in Animals

Levofloxacin is indicated in pediatric patients (6 months of age and older) only for the prevention of inhalational anthrax (post-exposure) and for plague [see Indications and Usage (1.13, 1.14)]. An increased incidence of musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) compared to controls has been observed in pediatric patients receiving levofloxacin [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 Infimitation take and used of the weight-bearing joints and other signs of arthropathy in immature asian solution as solution and the weight-bearing joints and other signs of arthropathy in immature animals of various species [see Animal Toxicology and/or immature animals of various species] and other signs of arthropathy in immature animals of various species [see Animal Toxicology and/or immature animals of various species] and other signs of arthropathy in immature animals of various species [see Animal Toxicology and/or immature animals of various species] and other signs of arthropathy in immature animals of various species [see Animal Toxicology and/or immature animals of various species] and the species of the set of the

Pharmacology (13.2)]. 5.11 Blood Glucose Disturbances As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with levofloxacin, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful

monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with levofloxacin, levofloxacin should be discontinued and appropriate therapy should be initiated immediately [see Adverse Reactions (6.2), Drug Interactions (7.3) and Patient Counseling formation (17.4)].

5.12 Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, 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, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if photosensitivity/phototoxicity occurs [see Adverse Reactions (6.3) and Patient Counseling Information (17.3)

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

6 ADVERSE REACTIONS

6.1 Serious and Otherwise Important Adverse Reactions The following serious and otherwise important adverse drug reactions are discussed in greater detail in other sections of labeling:

• Tendon Effects [see Warnings and Precautions (5.1)] tendon Effects [see Warnings and Precautions (5.1)]
 Exacerbation of Myasthemia 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 (5.5)] Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.7)] Peripheral Neuropathy that may be investible (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)]

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 < 55 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 does 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% cat patients treated with the 250 ng and 500 mg does and 5 4% of patients treated with the 750 mg does. The most common adverse drug reactions eading to discontinuation with the 250 and 500 mg does 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 does were gastrointestinal (1.4%), primarily nausea (0.6%); vomiting (0.4%); dizziness (0.3%); and nausea (0.6%), vomiting (0.5%); dizziness (0.3%); and headache (0.3%).

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

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

System/Organ Class	Adverse Reaction	% (N = 7,537)
Infections and Infestations	moniliasis	1
Psychiatric Disorders	insomnia* [see Warnings and Precautions (5.6)]	4
Nervous System Disorders	headache	6
	dizziness [see Warnings and Precautions (5.6)]	3
Respiratory, Thoracic and Mediastinal Disorders	dyspnea [see Warnings and Precautions (5.3)]	1
Gastrointestinal Disorders	nausea	7
	diarrhea	5
	constipation	3
	abdominal pain	2
	vomiting	2
	dyspepsia	2
Skin and Subcutaneous Tissue Disorders	rash [see Warnings and Precautions (5.3)]	2
	pruritus	1
Reproductive System and Breast Disorders	vaginitis	1†
General Disorders and Administration Site	edema	1
Conditions	injection site reaction	1
	chest pain	1

Table 5: Less Common (0.1 to 1%) Adverse Reactions Reported in Clinical Trials with Levofloxacin (N=7.537)

System/Organ Class	Adverse Reaction
Infections and Infestations	genital moniliasis
Blood and Lymphatic System Disorders	anemia thrombocytopenia granulocytopenia [see Warnings and Precautions (5.4)]
Immune System Disorders	allergic reaction [see Warnings and Precautions (5.3, 5.4)]
Metabolism and Nutrition Disorders	hyperglycemia hypoglycemia [see Warnings and Precautions (5.11)] hyperkalemia
Psychiatric Disorders	anxiety agitation confusion depression hallucination nightmare* [see Warnings and Precautions (5.6)] sleep disorder* anorexia abnormal dreaming*
Nervous System Disorders	tremor convulsions [see Warnings and Precautions (5.6)] paresthesia [see Warnings and Precautions (5.8)] vertigo hypertonia hypertonia hypertonia abnormal gait somnolence* syncope
Respiratory, Thoracic and Mediastinal Disorders	epistaxis
Cardiac Disorders	cardiac arrest palpitation ventricular tachycardia ventricular arrhythmia
Vascular Disorders	phlebitis
Gastrointestinal Disorders	gastritis stomatitis pancreatitis esophagitis gastroenteritis glossitis pseudomembranous/ <i>C. difficile</i> colitis [see Warnings and Precautions (5.7)]
Hepatobiliary Disorders	abnormal hepatic function increased hepatic enzymes increased alkaline phosphatase
Skin and Subcutaneous Tissue Disorders	urticaria [see Warnings and Precautions (5.3)]
Musculoskeletal and Connective Tissue Disorders	arthralgia tendinitis <i>[see Warnings and Precautions (5.1)]</i> myalgia skeletal pain
Renal and Urinary Disorders	abnormal renal function acute renal failure (see Warnings and Precautions (5.4))

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)]

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 fluoroquinolone, including levofloxacin, may increase the risk of

CNS stimulation and convulsive seizures [see Warnings and Precautions (5.6)]. 7.5 Theophylline No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a

Initial 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,

.6 Cyclosporii

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_{max} and k_x were slightly lower while T_{max} and t_x were slightly lower while the patient population presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered to be clinically significant. Therefore, no dosage adjustment is required for levofloxacin or cyclosporine when administered concomitantly.

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

7.8 Probenecid and Cimetidine

No significant effect of probenecid or cimetidine on the C_{max} of levofloxacin was observed in a clinical study involving healthy volunteers. The AUC and t_x of levofloxacin were higher while CL/F and CL_x 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 fluoroquinolones, including levofloxacin, may produce false-positive urine screening results for opiates using commercially available nmunoassay kits. Confirmation of positive opiate screens by more specific methods may be necessar

8 USE IN SPECIFIC POPULATIONS

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

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

8.3 Nursing Mothers

8.4 Pediatric Use

Based on data on other fluoroquinolones and very limited data on levofloxacin, it can be presumed that levofloxacin will be excreted in human based on data of home hadright motions and year made data on revense that in the previous data whether to milk. Because of the poleratial for services 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 (5.10) and Animal Toxicology and/or Pharmacology (13.2)].

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

4 CONTRAINDICATIONS
Levofloxacin is contraindicated in persons with known hypersensitivity to levofloxacin, or other of

500 mg, in flexible container, 30 mL fill
500 mg, in flexible container, 100 mL fill
750 mg, in flexible container, 150 mL fill

ner quinolone antibacterials [see Warnings and Precautions

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
of therapy.

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

As with other drugs in this class, some isolates of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with Levolution and a manufactory of the second second second second many develop resistance rainy reprojection and the second s

1.1 Nosocomial Pneumonia

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

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

Levofioxacin 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), 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimetho

1.3 Community-Acquired Pneumonia: 5-day Treatment Regimen

Levofioxaria is indicated for the treatment of community-acquired pneumonia due to Streptococcus pneumoniae (excluding multi-drug-resistant isolates [MDRSP]), Haemophilus influenzae, Haemophilus parainfluenzae, Mycoplasma pneumoniae, or Chlamydophila pneumoniae [see Dosage and Administration (2.1) and Clinical Studies (14.3)].

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, Haemophilus influenzae, or Moraxella catarrhalis [see Clinical Studies (14.4)].

1.5 Acute Bacterial Exacerbation of Chronic Bronchitis

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

Levofloxacin is indicated for the treatment of complicated urinary tract infections due to Escherichia coli. Klebsiella pneumoniae, or Proteus mirabilis [see Clinical Studies (14,7)].

Levofloxacin is indicated for the treatment of uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis,

evofloxacin is indicated for the treatment of chronic bacterial prostatitis due to Escherichia coli, Enterococcus faecalis, or methicillin-susceptible

furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible Staphylococcus aureus, or Streptococcus pyoge

1.10 Complicated Urinary Tract Infections: 10-day Treatment Regimen

1.9 Complicated Urinary Tract Infections: 5-day Treatment Regimen

Levofloxacin is indicated for the treatment of complicated unnary 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)].

1.7 Uncomplicated Skin and Skin Structure Infections

Staphylococcus epidermidis [see Clinical Studies (14.6)].

1.11 Acute Pyelonephritis: 5 or 10-day Treatment Regimen Levofloxacin is indicated for the treatment of acute pyelonephritis caused by Escherichia coli, including cases with concurrent bacteremia [see Clinical Studies (14.7, 14.8)].

1.12 Uncomplicated Urinary Tract Infections

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

1.13 Inhalational Anthrax (Post-Exposure)

1.8 Chronic Bacterial Prostatitis

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 postediatric patients for durations of therapy beyond 24 days has not been studied. Prolonged levofloxacin therapy should only be used when the benefit outweighs the risk [see Dosage and Administration (2.1, 2.2) and Clinical Studies (14.9)].

1.14 Plague

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

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)]

- vasculitis; arthralgia; myalgia; serum sicknes
 allergic pneumonitis;
- interstitial nephritis; acute renal insufficiency or failure;
- · hepatitis; jaundice; acute hepatic necrosis or failure;

5.4 Other Serious and Sometimes Fatal Reactions

anemia, including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities.

· fever, rash, or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome);

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

5.5 Hepatotoxicity

Post-marketing reports of severe hepatotoxicity (including acute hepatitis and fatal events) have been received for patients treated with levofloxacin. No evidence of serious drug-associated hepatotoxicity was detected in clinical trials of over 7,000 patients. Severe hepatotoxicity generally occurred within 14 days of initiation of therapy and most cases occurred within 6 days. Most cases of severe hepatotoxicity were not associated with hypersensitivity [see Warnings and Precautions (5.4)]. The majority of fatal hepatotoxicity reports occurred in patients 65 years of age or older and most were not

xacin to pediatric patients is appropriate. The safety of levof 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 assessment indicates that administration of levofloxacin to pediatric patients is appropriate (see Indications and Usage (1.14), Dosage and stration (2.2) and Clinical Studies (14.10)].

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

Adverse Events. In clinical trials, 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 musculoskeletal disorders when compared to the non-fluoroguinolone-treated children as illustrated in Table

Table 7: Incidence of Musculoskeletal Disorders in Pediatric Clinical Trial

Follow-up Period	Levofloxacin N = 1,340	Non-Fluoroquinolone* N = 893	p-value [†]
60 days	28 (2.1%)	8 (0.9%)	p = 0.038
1 year [‡]	46 (3.4%)	16 (1.8%)	p = 0.025

Non-Fluoroquinolone: ceftriaxone, amoxicillin/clavulanate, clarithromvcin

2-sided Fisher's Exact Test

There were 1,199 levolfoxacin-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 nusculoskeletal disorders resolved without sequela

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.

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

 • usuate i visuate i visuat	 • juning • ingling • unpling • unpling • unpling • unpling • weakness The neve damage may be permanent. Serious heart rhythm changes (QT prolongation and tonsades de pointes) Tall your hastbcare provider right away if you have a change in your hartbeat (a fast or irregular heartbeat), or if you faint. Levofloxacin in 5% Dextrose lipection may cause a rare propher provider right away if you have a change in your hartbeat (a fast or irregular heartbeat and can be very dangerous. The chances of this happening are higher in people. • who are soled? • who are soled? • who are soled? • who are coled you have a fully provider right away if you have a change in your hartbeat? • Who are coled you have a prolongation of the QT interval. • who are coled? • who are coled you have in they have a fully on the art hythm (antarhythmics) • Unterpose in bood sugar • the take or and they are than medicines to control heart rhythm (antarhythmics) • Other poblems with joints and tissues around joints in children can happen. Tell your child's healthcare provider if your child has any joint problems during or after treatment with Levofloxacin in 5% Dextrose injection and other fluoroquinotone medicines with oral ant-fdiabetes medicines or with insulin can get low blood sugar (hypoglycemia) and high blood sugar (hypedlycemia). Follow your healthcare provider instructions for how of the hold charge and you get low blood sugar (hypoglycemia) and high blood sugar (hypedlycemia). Follow you'r healthcare provider instructions for how of the hold charge and you get low blood sugar (hypoglycemia) and high blood sugar (hypedlycemia). Follow you'r healthcare provider instructions for how of an todice so and you get low blood sugar	 • Iching • Intervines of universe of your eyes Stop taking Levoftoxacin in 5% Destrose lipiction and tell your healthcare provider right away if you have yellowing of your skin or white part of your eyes, or if you have dark urine. These can be signs of a serious reaction to Levoftoxacin in 5% Destrose lipiction (a liver problem). • Central Nervous System Effects. Seizures have been reported in people who take fluoroquinolone antibiotics including Levoftoxacin in 5%. Destrose lipiction. Tell your healthcare provider right away if you have a history of sizures. Ask your healthcare provider whether taking Levoftoxacin in 5% Destrose lipiction. Tak to your healthcare provider right away if you get any of these side effects. The heaviors in ord or behavior. • Seizures • Intel ensities • Intervises see things, or sense things that individue (prancia) • Intervises • Intervise in produce whether a half to se of Levoftoxacin in 5%. Destrose lipiction. Tak to your healthcare provider right away if i you get any of the subscience. • Intervise in the charlows or nervous • Intervise in infection (Pseudomembranous colits) • Intervise in infection in and, lega, or the carn happen with many antibiotis. including Levoftoxacin in 5%. Destrose injection. Cal your healthcare provider right away if you get wellery diarrhea. Taking the first does not go away, or bloody stools. You may antibiotis, including Levoftoxacin in 5%. Destrose injection. Stop Levoftoxacin have finished your antibiotic. • Changes in sensation and nerve damage (Peripheral Neuropathy) Destrose injection. Taking and the first away if you get any of the following symptoms of peripheral neuropathy in your arms, hands, legs, or feet: • Paedomembranes in and, lega, or the claran happen in people taking fluoroquinolones, including Levoftoxacin in 5%. Destrose lipiction. Stop Levoftoxacin in 5%. Destrose lipiction. Stop Levoftoxacin i	What are the possible side effects of Levofloxacin in 5%. Dextrose lnjection? See "What is the most important information I should know about Levofloxacin in 5%. Dextrose lnjection?" Nee What is the most important information I should know about Levofloxacin in 5%. Dextrose lnjection?" Important in 5%. Dextrose lnjection and get emergency medical help right away if you have any of the following symptoms of a severe allergic reactions to the proble baking Levofloxacin in 5%. Dextrose lnjection?" Important in 5%. Dextrose lnjection and get emergency medical help right away if you have any of the following symptoms of a severe allergic reaction: Import in the most important in 5%. Dextrose lnjection even after only 1 dose. Stop taking Levofloxacin in 5%. Dextrose lnjection at the first sign of a skin rash and levofloxacin in 5%. Dextrose lnjection even after only 1 dose. Stop taking Levofloxacin at the first sign of a skin rash and call your healterare provider. Skin rash may be a sign of a more serious reaction to Levofloxacin in 5%. Dextrose lnjection. . Liver damage (hepatotoxicity): Hepatotoxicity can happen in people who take Levofloxacin in 5%. Dextrose lnjection. Call your healthcare provider right away if you have are serious reaction to Levofloxacin in 5%. Dextrose lnjection. . Iver damage (hepatotoxicity): Hepatotoxicity can happen in people who take Levofloxacin in 5%. Dextrose lnjection. Call your healthcare provider right away if you have early of a poeting is nore serious and in 5%. Dextrose lnjection. . Iver damage (hepatotoxicity): Hepatotoxicity can happen in people who take Levofloxacin in 5%. Dextrose lnjection. Call your healthcare pr
 A Geriatric patients are at increased risk for developing severe tendon disorders including tendon rupture when being treated with a fluoroquinolome salvedhozacin. This risk is further increased in patients receiving concomitant corticosteroid herapy. Tendinitis or tendon rupture can runy to tendon rupture accur during or after completion of therapy. Cases occurring up to several months after fluoroquinolone treatment threa been reported. Caution should be used when preservating levelfoxacin and eclefy patients several defer patients (20%) were > 65 several and several differences in salved vacanicing several endon (1); and Adverse Reactions (6.3). In phase 3 dinical triats. 1.945 levoftoxacin-treated patients (20%) were > 65 several and Reds patients (12%) were > 65 several and rung twere > 65 several and Reds patients (12%) were > 65 several and rung twere > 65 severe > 750 rung Tabler to . Ederly patients may be	Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure. Standardized procedures are based on a dilution method ^{1,24} (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the criteria outlined in Table 9. Diffusion techniques: Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure ^{2,3} requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5 mcg levofloxacin to test the susceptibility of bacteria to levofloxacin. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5 mcg levofloxacin disk should be interpreted according to the criteria outlined in Table 9. Minimum Inhibitory Disk Diffusion (zone diameter in mm) Minimum Inhibitory Disk Diffusion Concentrations (mcg/mL) Disk Diffusion Disk Diffusion Concentrations (mcg/mL) Disk Diffusion <t< td=""><td>Table 14: Clinical Success and Bacteriologic Eradication Rates for Resistant Streptococcus pneumoniae (Community-Acquired Pneumonia) Type of Resistance Clinical Success Bacteriologic Eradication Resistant to 2 antibacterials 17/18 (94.4%) 17/18 (94.4%) Resistant to 3 antibacterials 14/15 (93.3%) 14/15 (93.3%) Resistant to 4 antibacterials 7/7 (100%) 7/7 (100%) Resistant to 5 antibacterials 0 0 Bacteremia with MDRSP 8/9 (89%) 8/9 (89%) HAS Community-Acquired Pneumonia: 5-day Treatment Regimen To evaluate the safety and efficacy of the higher does and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiogically determine 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% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the levofloxacin 500 mg group. The 95% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the devofloxacin 500 mg group. The 95% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the levofloxac</td><td> Mean (SD) steady-state AUC_{0.54} was 33.4 ± 3.2 mcg+h/mL (range 30.4 to 36 mcg-h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post-exposure was significantly lower (1/10), compared to the placebo group (9/10) (P=0.0011, 2-sided Fisher's Exact Test). The one levofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period. 14.10 Plague Efficacy studies of levofloxacin could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [see Indications and Usage (1.14) and Dosage and Administration (2.1, 2.2)]. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady-state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0.51}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg+h/mL, respectively. The predicted steady-state peak plasma concentration in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally very 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally on daily [see Clinical Pharmacology (12.3)]. A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD_{0.50} (range 3 to 145 LD_{0.50}) of Yersinia pestis (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofl</td></t<>	Table 14: Clinical Success and Bacteriologic Eradication Rates for Resistant Streptococcus pneumoniae (Community-Acquired Pneumonia) Type of Resistance Clinical Success Bacteriologic Eradication Resistant to 2 antibacterials 17/18 (94.4%) 17/18 (94.4%) Resistant to 3 antibacterials 14/15 (93.3%) 14/15 (93.3%) Resistant to 4 antibacterials 7/7 (100%) 7/7 (100%) Resistant to 5 antibacterials 0 0 Bacteremia with MDRSP 8/9 (89%) 8/9 (89%) HAS Community-Acquired Pneumonia: 5-day Treatment Regimen To evaluate the safety and efficacy of the higher does and shorter course of levofloxacin, 528 outpatient and hospitalized adults with clinically and radiogically determine 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% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the levofloxacin 500 mg group. The 95% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the devofloxacin 500 mg group. The 95% Cl for the difference of response rates (levofloxacin 750 minus levofloxacin 500 mg group and 91.1% in the levofloxac	 Mean (SD) steady-state AUC_{0.54} was 33.4 ± 3.2 mcg+h/mL (range 30.4 to 36 mcg-h/mL). Mortality due to anthrax for animals that received a 30 day regimen of oral levofloxacin beginning 24 hrs post-exposure was significantly lower (1/10), compared to the placebo group (9/10) (P=0.0011, 2-sided Fisher's Exact Test). The one levofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period. 14.10 Plague Efficacy studies of levofloxacin could not be conducted in humans with pneumonic plague for ethical and feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The mean plasma concentrations of levofloxacin associated with a statistically significant improvement in survival over placebo in an African green monkey model of pneumonic plague are reached or exceeded in adult and pediatric patients receiving the recommended oral and intravenous dosage regimens [see Indications and Usage (1.14) and Dosage and Administration (2.1, 2.2)]. Levofloxacin pharmacokinetics have been evaluated in adult and pediatric patients. The mean (± SD) steady-state peak plasma concentration in human adults receiving 500 mg orally or intravenously once daily is 5.7 ± 1.4 and 6.4 ± 0.8 mcg/mL, respectively; and the corresponding total plasma exposure (AUC_{0.51}) is 47.5 ± 6.7 and 54.6 ± 11.1 mcg+h/mL, respectively. The predicted steady-state peak plasma concentration in pediatric patients ranging in age from 6 months to 17 years receiving 8 mg/kg orally very 12 hours (not to exceed 250 mg per dose) were calculated to be comparable to those observed in adults receiving 500 mg orally on daily [see Clinical Pharmacology (12.3)]. A placebo-controlled animal study in African green monkeys exposed to an inhaled mean dose of 65 LD_{0.50} (range 3 to 145 LD_{0.50}) of Yersinia pestis (CO92 strain) was conducted. The minimal inhibitory concentration (MIC) of levofl

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 excited 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)].

Pla 12 18 24 30 36

		linimum Inhibito centrations (mcg	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 ⁴	≤ 0.25					
Bacillus anthracis ⁴	≤ 0.25					

African green monkeys. Trough concentrations of evolutions and evolution of a week of a single of ormal ministerin anged form 2.04 to 3.5 meg/minima and African green monkeys. Trough concentrations at 24 hours post-dose ranged from 4.03 to 0.06 mcg/minimation. Mean (50) AUC_{0.24} 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 levoffoxacin or placebo beginning within 6 hrs of the onset of telemetered fever (≥ 39°C for more than 1 hour). Mortality in the levoftoxacin group was significantly lower (1/17) compared to the placebo group (7/7) [p-0.001, Fisher's Exact Test; exact Test; exact Ste's confidence interval (-9.93%, -55.5%) for the difference n mortality]. One levofloxacin-treated animal was euthanized on Day 9 post-exposure to Y. pestis due to a gastric o

Clinical and Laboratory Standards Institute (CLSI). Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically. Cuinical and Laboratory Standards Institute (CLS)). Methods for Dilution Antimicrobial Susceptibility lests for Bacteria That Grow Aerobically. Approved Standard-9th ed. CLSI Document M7-A9, CLSI, 950 West Valley Rd., Suite 2500, Wayne, PA, 2012. CLSI. Performance Standards for Antimicrobial Susceptibility Testing, 22th Informational Supplement. CLSI Document M100-S22, 2012. CLSI. Performance Standards for Antimicrobial Disk Susceptibility Testing, 22th Informational Supplement. CLSI Document M100-S22, 2012. CLSI. Nethods for Antimicrobial Dilution and Disk Susceptibility Testing of Infrequently Isolated or Fastidious Bacteria; Approved Guideline-2th ed. Cl SI. Document M46, 20, 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).

250 mg, in flexible container, 50 mL fill.

500 mg, in flexible container, 100 mL fill

750 mg, in flexible container, 150 mL fill.

Strength

5 mg per mL

5 mg per mL

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.

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

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

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

endon disorders with fluoroquinolones is higher in older patients usually over 60 years of age, in patients taking corticosteroid

Exacerbation of Myasthenia Gravis: Patients should inform their physician of any history of myasthenia gravis. Patients should notify their

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

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.

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

problems before taking this drug. Parents of pediatric patients should also notify their child's physician of any tendon or joint-related problems

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

Patients given levofloxacin for these conditions should be informed that efficacy studies could not be conducted in humans for ethical and

ionitored for evidence of bleeding, and also have their anticoagulation tests closely monitored while taking warfarin co

feasibility reasons. Therefore, approval for these conditions was based on efficacy studies conducted in animals.

The brand names mentioned in this document are the trademarks of their respective owners.

Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin, be

that occur during or following levofloxacin therapy [see Warnings and Precautions (5.10) and Use in Specific Populations (8.4)].

Musculoskeletal Disorders in Pediatric Patients: Parents should inform their child's physician if their child has a history of joint-related

Convulsions: Convulsions have been reported in patients taking fluoroquinolones, including levofloxacin. Patients should notify their

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

15 REFERENCES

315550

315565

315560

2nd ed. CLSI Document M45-A2, 2010.

17 PATIENT COUNSELING INFORMATION See FDA-Approved Medication Guide (17.6)

17.1 Antibacterial Resistance

17.2 Administration with Fluids

of an allergic reaction

hould contact their physiciar

7.5 Plague and Anthrax Studies

lanufactured for

Fresenius Kabi USA, LLC

Lake Zurich, IL 60047

Revised: March 2015

Made in Norway

451218B

17.3 Serious and Potentially Serious Adverse Reactions

drugs, and in patients with kidney, heart or lung transplants.

physician before taking this drug if they have a history of convulsions

interval, including prolonged heart palpitations or a loss of consciousness.

physician if they experience any symptoms of muscle weakness, including respiratory difficulties

16 HOW SUPPLIED/STORAGE AND HANDLING

63323-355-50

63323-355-65

63323-355-60

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

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

8.7 Hepatic Impairment

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

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

Levofloxacin exhibits a low potential for acute toxicity. Mice, rats, dogs and monkeys exhibited the following clinical signs after receiving a single high dose of levofloxacin: ataxia, ptosis, decreased locomotor activity, dyspnea, prostration, tremors, and convulsions. Doses in excess of 1,500 mg/kg orally and 250 mg/kg IV produced significant mortality in rodents.

11 DESCRIPTION

evofloxacin in 5% dextrose injection is a synthetic broad-spectrum antibacterial agent for intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9fluoro-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



C₁₀H₂₀FN₂O₄ • ½ H₂O

Levofloxacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine

M.W. 370.38

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⁻³>Cu⁻²>An⁻²>Mg^{+2>}Ca⁻².

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 Levofloxacin Injection Premix in Single-Use Flexible Containers is a sterile, preservative-free aqueous solution of levofloxacin with pH ranging form 3.8 to 5.8. This is a diffue, non-pyrogenic, nearly isotonic premised solution that contains levofloxacin in 5% Dextrose (D5W). Solu 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 (free/lex[®] bag). The amount of water that can permeate from the container into the overwrap is insufficient to affect 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

12 CLINICAL PHARMACOLOGY

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

12.3 Pharmaco

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

Table 8: Mean ± SD Levofloxacin PK Parameters

Regimen	C _{max} (mcg/mL)	T _{max} (h)	AUC (mcg•h/mL)	CL/F ¹ (mL/min)	Vd/F ² (L)	t _{1/2} (h)	CL _R (mL/min)			
Single dose										
250 mg oral tablet ³	2.8 ± 0.4	1.6 ± 1	27.2 ± 3.9	156 ± 20	ND	7.3 ± 0.9	142 ± 21			
500 mg oral tablet ^{3*}	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 ¹²	5.8 ± 1.8	0.8 ± 0.7	47.8 ± 10.8	183 ± 40	112 ± 37.2	7 ± 1.4	ND			
500 mg IV ³	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 IV⁵	11.5 ± 4 ⁴	ND	110 ± 40	126 ± 39	75 ± 13	7.5 ± 1.6	ND			
Multiple dose										
500 mg every 24h oral tablet ³	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 ³	6.4 ± 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 ⁶	8.7 ± 4 ⁷	ND	72.5 ± 51.2 ⁷	154 ± 72	111 ± 58	ND	ND			
750 mg every 24h oral tablet⁵	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 ⁸	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	166 ± 44	89 ± 13	7.5 ± 2.1	126 ± 38			
Female ⁹	7 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	136 ± 44	62 ± 16	6.1 ± 0.8	106 ± 40			
Young ¹⁰	5.5 ± 1	1.5 ± 0.6	47.5 ± 9.8	182 ± 35	83 ± 18	6 ± 0.9	140 ± 33			
Elderly ¹¹	7 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	121 ± 33	67 ± 19	7.6 ± 2	91 ± 29			
500 mg oral single dose tablet, patients with renal insufficiency:										
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			
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	ND	ND	51 ± 24	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

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



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 bitser 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 of 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 1.3 mcg/g over a 24-hour period after a single 500 mg oral dose.

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

Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes Level location is determined by allower in pleasing and unite and does not inter interactionary to ender the advanced in the ender of the second advanced in the second advanced in the second advanced interaction approximately 87% of an administered dose was recovered as unchanged drug in unite 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 unite 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 unite 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. Concomitant administration of either cimetidine or probenecif results in approximately 24% and 35% reduction in the lever0foxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in addition of the units addition to the glomerular filtration. Concomitant administration of either cimetidine or probenecif results in approximately 24% and 35% reduction in the lever0foxacin renal clearance, respectively, indicating that secretion of levofloxacin occurs in addition of the units amples freshly collected from subjects receiving occurs in the renal proximal tubule. No levofloxacin crystals were found in any of the units samples freshly collected from subjects receiving levofloxacin

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 plasme 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_{0.24} and C_{max}) to those observed in adult patients idministered 500 mg of levofloxacin once every 24 hours.

There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine The term of the significant consideration. Following a 500 mg oral dose of levoftoxacin to healthy male subjects intervine and the main and intervine and the subjects and the s 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)].

Hepatic Impairment

v tract or skir

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

Bacterial Infection

subiects. Drug-Drug Interactions The potential for pharmacokinetic drug interactions between levofloxacin and antacids, warfarin, theophylline, cyclosporine, digoxin, probenecid, and

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

12.4 Microbiology

Mechanism of Action Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the Leisomer. The mechanism of action of levelfoxacin and other fluorone animicrobial squite transcription inhibition of bacterial topologic gyrase (both of which are type II topolosomerases), enzymes required for DNA replication, transcription, repair and recombination.

Mechanism of Resistance

luoroquinolone 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^o to 10⁻¹⁰). Cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones uinolones may be susceptible to levofloxacin

Activity in vitro and in vivo Levofloxacin has in vitro activity against Gram-negative and Gram-positive bacteria.

cimetidine has been evaluated [see Drug Interactions (7)].

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

Gram-Positive Bacteria

Enterococcus faecalis Staphylococcus aureus (methicillin-susceptible isolates) phylococcus epidermidis (methicillin-susceptible isolates) Staphylococcus saprophyticus

Streptococcus pneumoniae (including multi-drug-resistant isolates [MDRSP1]) ococcus pyogenes

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 trimethopr

Gram-Negative Bacteria Enterobacter cloacae Escherichia coli

Haemophilus influenzae , ophilus parainfluenzae

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

Quality Control:

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

Table 10: Quality Control 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
Streptococcus pneumoniae	ATCC 49619	0.5 to 2	20 to 25

13 NONCLINICAL TOXICOLOGY

3.1 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/da/sy wa 1.4 times the highest recommended human dose (750 mg) based upon relative body surface area. Levofloxacin dd 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_{max} .

evofloxacin 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 schibited chinically severe arthropathy ir 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 and are not associated with nephrotoxicity

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

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

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

14.1 Nosocomial Pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a multi-center, randomized, open-label study comparing intravenous levologically occurrented resources in a presentational whole crimotical and a standard resources and a standard resource and the standard resource and 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 and the initial ini

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 response rates (levofloxacin minus comparator) was [-17.2, 12]. The microbiological eradication rates at the post-therapy visit were 66.7% for levofloxacin and 60.6% for comparator. The 95% CI for the difference of eradication rates (levofloxacin minus comparator) was [-8.3, 20.3]. Clinical success and bacteriological eradication rates by pathogen are detailed in Table 11

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

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

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

Adduit 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, non comparative trial of 500 mg levoltoxacit must comparation was points, in the second study, core paintened where the fore the project mathematic mathematic model in the second study is a second study of the second study of the second study is a second study of the second stu

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%)

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

14.4 Acute Bacterial Sinusitis: 5-day and 10 to 14 day Treatment Regimens Levofloxacin 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 is unsitis 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 parable 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

Pathogen	Levofloxacin 750 mg x 5 days	Levofloxacin 500 mg x 10 days
Streptococcus pneumoniae*	25/27 (92.6%)	26/27 (96.3%)
Haemophilus influenzae*	19/21 (90.5%)	25/27 (92.6%)
Moraxella catarrhalis*	10/11 (90.9%)	13/13 (100%)

14.5 Complicated Skin and Skin Structure Infections

abscesses. These rates were equivalent to those seen with comparator drugs.

overall eradication rates for pathogens of interest are presented in Table 17.

14.6 Chronic Bacterial Prostatitis

Pathogen

E. faecalis

S. epidermidis

active ciprofloxacin.

(cUTI or AP)

(cUTI or AP)

Pathogen

Escherichia coli

Klebsiella pneumoniae Proteus mirabilis

Evaluable) are summarized in Table 18.

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.

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB₂) 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 endpaining of an oronage of ing, once daily for a control of 20 days of an optional profession light was a 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

 Table 17: Bacteriological Eradication Rates (Chronic Bacterial Prostatitis)

Eradication

14 (93.3%)

39 (72 2%

9 (81.8%)

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

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 (546 patients) with ciprofloxacin 400 mg IV or 500 mg orally tivice daily for 10 days (563 patients). Patients with AP complicated

by underlying renal diseases or conditions such as complete obstruction, surgery, transplantation, concurrent infection or congenital malformation were "excluded." Efficacy was measured by bacteriologic eradication of the baseline organism(s) at the post-therapy visit in patients with a pathogen identified at baseline. The post-therapy (test-of-cure) visit occurred 10 to 14 days after the last active dose of levofloxacin and 5 to 9 days after the last dose of

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

Table 18: Bacteriological Eradication at Test-of-Cure

n/N

239/318

157/21

Ily Evaluable Population

215/241

144/165

71/76

Bacteriological Eradication Rate

(n/N)

* The mITT population included patients who received study medication and who had a positive (≥ 10⁵ CFU/mL) urine culture with no more than 2 uropathogens at baseline. Patients with missing response were counted as failures in this analysis.
* The Microbiologically Evaluable population included patients with a confirmed diagnosis of cUTI or AP, a causative organism(s) at baseline present

at ≥ 10⁵ CFU/mL, a valid test-of-cure urine culture, no pathogen isolated from blood resistant to study drug, no premature discontinuation or loss to

Bacteriologic eradication rates in the Microbiologically Evaluable population at TOC for individual pathogens recovered from patients randomized to

Table 19: Bacteriological Eradication Rates for Individual Pathogens Recovered from Patients Randomized to Levofloxacin 750 mg QD for 5

Days Treatment

Population

750 mg orally or IV once daily for 5 days 400 mg IV/500 mg orally twice daily for 10 days

Ciprofloxacin

75.2

89.2

93.4

Ciprofloxacin (N=125)

Eradication

9 (81.8%)

11 (78.6%)

Overall Difference

0.5 (-6.1, 7.1)

-3.2 [-8.9, 2.5]

[95% CI]

Levofloxacin-Ciprofloxad

Levofloxacin (N=136)

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

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

Levofloxacin

%

75.7

81.6

86

83.2

n/N

252/333

168/230

228/265

154/185 74/80

follow-up, and compliance with treatment (among other criteria

levofloxacin treatment are presented in Table 19.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and

6	500 mg every 48h for patients with moderate renal impairment (CLCR 20 to 50 mL/min) and infections of the respiratory
7	dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling
	healthy males 22 to 75 years of age
9	healthy females 18 to 80 years of age
10	young healthy male and female subjects 18 to 36 years of age
11	healthy elderly male and female subjects 66 to 80 years of age
12	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 volunteers, 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 to blowing a blowing a 50 mg or 750 mg or co-daily dosage regimens were approximately 5.7 ± 1.4 and 0.5 ± 0.2 mcg/mL after the 500 mg doses, and 8.6 ± 1.9 and 1.1 ± 0.4 mcg/mL after the 750 mg doses, respectively. The mean ± SD peak and trough plasma concentrations attained following and the set of the set 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).

Other Bacteria
Proteus mirabilis Pseudomonas aeruginosa Serratia marcescens
Legionella pneumophila Moraxella catarrhalis
Nepsiella prieuriorilae

Chlamydophila pneumoniae Mycoplasma pneumoniae

The following in vitro data are available, but their clinical significance is unknown; Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 mcg/mL or less against most (≥ 90%) isolates of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these bacteria have not been established in adequate and well-controlled clinical trials.

Gram-Positive Bacteria
Staphylococcus haemolyticus
β-hemolytic Streptococcus (Group C/F)
β-hemolytic Streptococcus (Group G)
Streptococcus agalactiae
Chronita an annua milleri

alactiae Viridans group streptococci Bacillus anthracis Gram-Negative Bacteria

Acinetobacter bauma Acinetobacter Iwoffii Bordetella pertussis Citrobacter koseri Citrobacter freundii nterobacter aerogenes Enterobacter sakazakii Klebsiella oxytoca Morganella morganii Pantoea agglomerans Proteus vulgaris Providencia rettgeri Providencia stuartii

Pseudomonas fluorescen Yersinia pestis

Anaerobic Gram-Positive Bacteria Clostridium perfringen

Susceptibility Tests

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

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

Pathogen	No. Pathogens	Bacteriological Eradication Rate (%)
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100

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

Levofloxacin was effective for the treatment of community acquired pneumonia caused by multi-drug-resistant Streptococcus pneumoniae (MDRSP) MDRSP isolates are isolates resistant to two or more of the following antibacterials: penicillin (MIC ≥ 2 mcg/mL), 2nd generation cephalosporins (e.g. cefuroxime, 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 Patients (Population Valid for Efficacy)

Screening Susceptibility	Clinical Success		Bacteriological Success*			
	n/N†	%	n/N‡	%		
Penicillin-resistant	16/17	94.1	16/17	94.1		
2nd generation Cephalosporin-resistant	31/32	96.9	31/32	96.9		
Macrolide-resistant	28/29	96.6	28/29	96.6		
Frimethoprim/ Sulfamethoxazole-resistant	17/19	89.5	17/19	89.5		
Tetracycline-resistant	12/12	100	12/12	100		
 n = the number of MDRSP isolates eradicated or presumed eradicated in microbiologically evaluable patients; N = number of MDRSP isolates in a designated resistance group. Not all isolates were resistant to all antimicrobial classes tested. Success and eradication rates are summarized in Table 14. 						

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

14.5 Complicated ormary fract intercions and Acture Pytoneprints: 10-ag irreatment regiment 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).

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

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 baseline (modified intent to treat or mITT) and the group of patients in the mITT population who closely followed the protocol (Micro Evaluable) are summarized in Table 20.

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

	Levofloxacin 250 mg once daily for 10 days		Ciprofloxacin 500 mg twice daily for 10 days	
	n/N	%	n/N	%
mITT Population [†]	174/209	83.3	184/219	84
Microbiologically Evaluable Population [‡]	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 response were counted as failures in this

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

14.9 Inhalational Anthrax (Post-Exposure)

14.5 immatutorial Antimax (POSt-Exposure) The effectiveness of levolfoxacin 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 sage (1.13) and Dosage and Administration (2.1, 2.2)].

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

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

In pediatric patients, the safety of levofloxacin for treatment durations of more than 14 days has not been studied. An increased incidence of mysculoskeletal adverse events (arthrataja, 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. The place of the strain) was conducted. The minimal initiation of the place of the strain of the strain was conducted. The minimal initiation of the place of the strain was conducted. The minimal initiation of the place of the strain was conducted at the study was 0.125 mcg/mL. In the animals studied, mean plasma concentrations of levofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady-state ranged from 2.79 to 4.87 mcg/mL. Steady-state trough concentrations at 24 hours post-dose ranged from 0.107 to 0.164 mcg/mL.