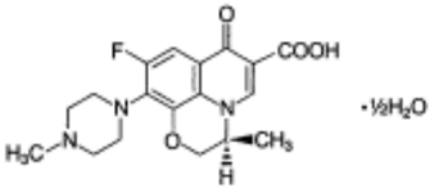
CRAVIT® I.V.
(levofloxacin hemihydrate)**Prescribing Information**

DESCRIPTION

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

The chemical structure is:



Its empirical formula is $C_{18}H_{20}FN_3O_4$ ⍰ ½ H_20 and its molecular weight is 370.38. Levoflocacin is a light yellowish-white to yellow-white crystal or crystalline powder. The molecule exists as a zwitterion at the pH conditions in the small intestine.

The data demonstrate that from pH 0.6 to 5.8, the solubility of levofloxacin 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: $Al^{+3}>Cu^{+2}>Zn^{+2}>Mg^{+2}>Ca^{+2}$.

COMPOSITON

Each 50 mL bottle of CRAVIT® i.v. solution (5mg/mL) contains 250 mg of levofloxacin as active ingredient. Each 100 mL bottle of CRAVIT® i.v. solution (5mg/mL) contains 500 mg of levofloxacin as active ingredient. The solution also contains the following ingredients: sodium chloride; sodium hydroxide; hydrochloric acid (qs: pH 4.8) and water of injection for a volume of 50 mL and 100 mL.

CLINICAL PHARMACOLOGY

The mean ± SD pharmacokinetic parameters of levofloxacin determined under single and steady state conditions following oral (p.o.) or intravenous (i.v.) doses of levofloxacin are summarized in Table 1.

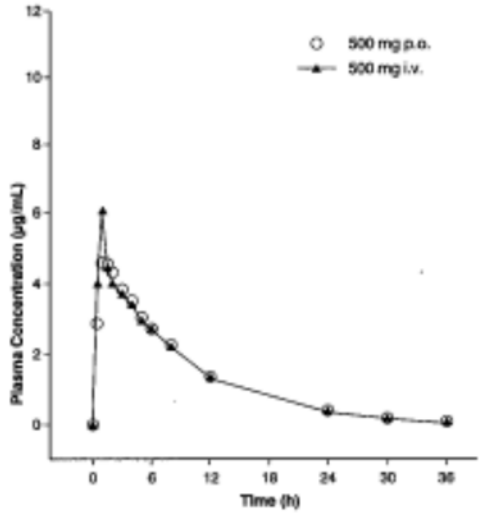
Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg tablet and a 750 mg tablet of levofloxacin are both approximately 99%, demonstrating complete oral absorption of levofloxacin. Following a single intravenous dose of levofloxacin to healthy volunteers, the mean±SD peak plasma concentration attained was 6.2 ± 10 µg/mL after a 500 mg dose infused over 60 minutes and 11.5± 4.0 µg/mL after a 750 mg dose infused over 90 minutes.

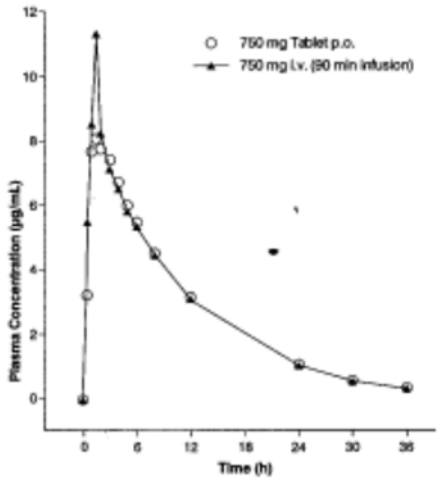
Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral/or i.v. dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen. The mean±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7± 1.4 and 0.5± 0.2 µg /mL after the 500 mg doses, and 8.6± 1.9 and 1.1± 0.4 µg/ mL after the 750 mg doses, respectively. The mean±SD peak and trough plasma concentrations attained following multiple once-daily i.v. regimens were approximately 6.4± 0.8 and 0.6± 0.2 µg /mL after the 500 mg doses, and 12.1± 4.1 and 1.3± 0.71 µg /mL after the 750 mg doses, respectively.

The plasma concentration profile of levofloxacin after i.v. 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 i.v. routes of administration can be considered interchangeable. (See following chart.)

Mean Levofloxacin Plasma Concentration: Time Profiles



Mean Levofloxacin Plasma Concentration: Time Profiles



Distribution

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

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

Metabolism

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

Excretion

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

Special Populations

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

Pediatric: The pharmacokinetics of levofloxacin in pediatric subjects have not been studied.

Gender: There are no significant differences in levofloxacin pharmacokinetics between male and female subjects when subjects' differences in creatinine clearance are taken into consideration. Following a 500 mg oral dose of levofloxacin to healthy male subjects, the mean terminal plasma elimination half-life of levofloxacin was about 7.5 hours, as compared to approximately 6.1 hours in female subjects. This difference was attributable to the variation in renal function status of the male and female subjects and was not believed to be clinically significant. Drug absorption appears to be unaffected by the gender of the subjects. Dose adjustment based on gender alone is not necessary.

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

Renal insufficiency: Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50 mL/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following hemodialysis or CAPD. (See **PRECAUTIONS: General** and **DOSAGE AND ADMINISTRATION.)**

Hepatic insufficiency: 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.

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

Drug – drug interactions: The potential for pharmacokinetic drug interaction between levofloxacin and theophylline, warfarin, cyclosporine, digoxin, probenecid, cimetidine, sucralfate, and antacids has been evaluated. (See **PRECAUTIONS: Drug Interactions**.)

Electrocardiogram

In a study of 48 healthy volunteers receiving single dosed of levofloxacin 500, 1000, and 1500 mg and placebo, a dose – related increase from baseline to post – dose of average QTc was observed. These changes were not statistically significant from placebo for the 500 mg dose, variably statistically significant for the 1000 mg dose depending on the correction method used, and statistically significant for the 1500 mg dose. (See **PRECAUTION: General**.)

Table 1. Mean± SD Levofloxacin PK Parameters

Regimen	C_{max} (ug/mL)	T_{max} (h)	AUC (Ug.h/mL)	CL/F[1] (mL/min)	Vd/F[2] (L)	t½ (h)	CL_R (mL/min)
Single dose							
250 mg p.o.[3]	2.8±0.4	1.6±1.0	27.2±3.9	156±20	ND	7.3±0.9	142±21
500 mg p.o[3*]	5.1± 0.8	1.3±0.6	47.9±6.8	178±28	ND	6.3±0.6	103±30
500 mg I.V.[3]	6.2±1.0	1.0±0.1	48.3±5.4	175±20	90±11	6.4±0.7	112±25
750 mg p.o.[5*]	9.3±1.6	1.6 ±0.8	101±20	129±24	83±17	7.5±0.9	ND
750 mg I.V.[5]	11.5±4.0 [4]	ND	110±40	126±39	75±13	7.5±1.6	ND
Multiple dose							
500 mg q24h p.o.[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 q24h i.v.[3]	6.4±0.8	ND	54.6±11.1	158±29	91±12	7.0±0.8	99±28
500 mg or 250 mg q24h i.v.	8.7±4.0[7]	ND	72.5±51.2[7]	154±72	111±58	ND	ND
Patients with bacterial infection[6]							
750 mg q24h p.o.[5]	8.6±1.9	1.4±0.5	90.7±17.6	143±29	100±16	8.8±1.5	116±28
750 mg q24h i.v.[5]	12.1±4.1[4]	ND	108±34	126±37	80±27	7.9±1.9	ND
500 mg p.o. single dose, effects of gender and age:							
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]	7.0±1.6	1.7±0.5	67.7±24.2	136±44	62±16	6.1± 0.8	106±40
Young[10]	5.5±1.0	1.5±0.6	47.5±9.8	182±35	83±18	6.0 ±0.9	140±33
Elderly[11]	7.0 ±1.6	1.4 ±0.5	74.7±23.3	121±33	67 ±19	7.6±2.0	91±29
500 mg p.o. single dose, patients with renal insufficiency:							
CL_{CR} 50-80 mL/min	7.5±1.8	1.5±0.5	95.6 ±11.8	88±10	ND	9.1±0.9	57±8
CL_{CR} 20-49 mL/min	7.1±3.1	2.1±1.3	182.1± 62.6	51±19	ND	27±10	26±13
CL_{CR} <20 mL/min	8.2±2.6	1.1±1.0	263.5 ±72.5	33±8	ND	35±5	13±3
hemodialysis	5.7±1.0	2.8±2.2	ND	ND	ND	76±42	ND
CAPD	6.9±2.3	1.4±1.1	ND	ND	ND	51±24	ND

[1]clearance/bioavailability

[2]volume of distribution/bioavailability

[3]healthy males 18-53 years of age

[4]60 min infusion for 250 mg and 500 mg doses, 90 min infusion for 750 mg dose

[5]healthy male and female subjects 18-54 years of age

[6]500 mg q48h for patients with moderate renal impairment (CL_{CR} 20-50 mL/min) and infections of the respiratory tract or skin

[7]dose-normalized values (to 500 mg dose), estimated by population pharmacokinetic modeling

[8]healthy males 22-75 years of age

[9]healthy females 18-80 years of age

[10]young healthy male and female subjects 18-36 years of age

[11] healthy elderly male and female subjects 66-80 years of age

*Absolute bioavailability; F=0.99 ±0.08 from a 500 –mg tablet and F=0.99±0.06 from a750–mg tablet ND = not determined.

MICROBIOLOGY

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

Levofloxacin has in vitro activity against a wide range of gram- negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

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

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

Levofloxacin has been shown to be active against most strains of the following microorganisms both in vitro and in clinical infections as described in the **INDICATIONS AND USAGE** section:

Aerobic gram – positive microorganisms

Enterococcus faecalis (may strains are only moderately susceptible)
Staphylococcus aureus (methicillin- susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including penicillin resistant strains**)
Streptococcus pyogenes
*Note: penicillin – resistant S. *pneumonia*e are those strains with a penicillin MIC value of ≥2µg/mL.

Aerobic gram – negative microorganisms

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus parainfluenzae
Klebsiella pneumoniae
Legionella pneumophila
Moraxella catarrhalis
Proteus mirabilis
Pseudomonas aeruginosa

As with other drugs in this class, some strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin.

Other microorganisms
Chlamydia pneumonia
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 μg/mL or less against most (≥90 %) strains of the following microorganisms; however, the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive micreorganisms

Staphylococcus epidermidis (methicillin-susceptible strains)
Streptococcous (Group C/F)
Streptococcus (Group G)
Streptococcus agalactiae
Streptococcus milleri
Viridans group streptococci

Aerobic gram-negative microorganisms

Acinetobacter baumannii
Acinetobacter lwoffii
Bordetella pertussis
Citrobacter (diversus) koseri
Citrobacter freundii
Enterobacter aerogenes
Enterobacter sakazakii
Klebsiella oxytoca
Morganella morganii
Pantoea (Enterobacter) agglomerans
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens

Anaerobic gram-positive microorganisms

Clostridium perfringens

Susceptibility Tests

Susceptibility testing for levofloxacin should be performed, as it is the optimal predictor of activity.

Dilution techniques: Quantitative methods are used to determine antimicrobial minimal inhibitory concentrations (MIC values). These MIC values 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] (broth or agar) or equivalent with standardized inoculum concentrations and standardized concentrations of levofloxacin powder. The MIC values should be interpreted according to the following criteria:

For testing aerobic microorganisms other than *Haemophilus influenza, Haemophilus parainfluenzae*, and *Streptococcus spp.* Including S.*pneumoniae:*

MIC (μg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

For testing *Haemophilus influenzae* and *Haemophilus parainfluenzae*: [a]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)

[a] These interpretive standards are applicable only to broth microdilution susceptibility testing with *Haemophilus influenzae* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[1]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding MIC results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For testing *Streptococcus* spp. Including S. *pneumonia*: [b]

MIC (µg/mL)	Interpretation
≤2	Susceptible (S)
4	Intermediate (I)
≥8	Resistant (R)

[b]These interpretive standards are applicable only to broth microdilution susceptibility tests using cation-adjusted Mueller-Hinton broth with 2-5% lysed horse blood.

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

Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. Standard levofloxacin powder should give the following MIC values:

Microorganism		MIC (µg/mL)
Enterococcus faecalis	ATCC 29212	0.25-2
Escherichia coli	ATCC 25922	0.008-0.06
Escherichia coli	ATCC 35218	0.015 – 0.06
Pseudomonas aeruginosa	ATCC 27853	0.5-4
Staphylococcus aureus	ATCC 29213	0.06 -0.5
Haemophilus influenzae	ATCC 49247[c]	0.008 – 0.03
Streptococcus pneumoniae	ATCC 49619[d]	0.5 - 2

[c] This quality control range is applicable to only H. *influenza* ATCC 49247 tested by a broth microdilution procedure using Haemophilus Test Medium (HTM).[1]

[d] This quality control range is applicable to only *S. pneumonia* ATCC 49619 tested by a broth microdilution procedure using cation-adjusted Mueller Hinton broth with 2-5 % lysed horse blood.

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] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 5-µg levofloxacin to test the susceptibility of microorganisms to levofloxacin.

Reports from the laboratory providing results of the standard single-disk susceptibility test with a 5-µg levofloxacin disk should be interpreted according to the following criteria:

For aerobic microorganisms other than *Haemophilus influenza*, *Haemophilus parainfluenzae*, and *Streptococcus* spp. Including *S.pneumoniae:*

Zone diameter (mm)	Interpretation
≥17	Susceptible(S)
14-16	Intermediate (I)
≤13	Resistant (R)

For *Haemophilus influenza* and *Haemophilus parainfluenzae*: [e]

Zone diameter (mm)	Interpretation
≥17	Susceptible(S)

[e] These interpretive standards are applicable only to disk diffusion susceptibility testing with *Haemophilus influenza* and *Haemophilus parainfluenzae* using Haemophilus Test Medium.[2]

The current absence of data on resistant strains precludes defining any categories other than "Susceptible." Strains yielding zone diameter results suggestive of a "nonsusceptible" category should be submitted to a reference laboratory for further testing.

For *Streptococcus* spp. Including S.*pneumoniae*: [f]

Zone diameter (mm)	Interpretation
≥17	Susceptible(S)
14-16	Intermediate (I)
≤13	Resistant (R)

[f] These zone diameter standards for *Streptococcus* spp. Including S.*pneumoniae* apply only to tests performed using Mueller- Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for levofloxacin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures. For the diffusion technique, the 5-ug levofloxacin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone Diameter (mm)
Escherichia coli	ATCC 25922	29-37
Pseudomonas aeruginosa	ATCC 27853	19-26
Staphylococcus aureus	ATCC 25923	25-30
Haemophilus influenzae	ATCC 49247[g]	32-40
Streptococcus pneumoniae	ATCC 49619[h]	20-25

[g] This quality control range is applicable to only H. *influenzae* ATCC 49247 tested by a disk diffusion procedure using Haemophilus Test Medium (HTM). [2]

[h] This quality control range is applicable to only S. *pneumonia* ATCC 49619 tested by a disk diffusion procedure using Mueller – Hinton agar supplemented with 5% sheep blood and incubated in 5% CO_2.

INDICATIONS AND USAGE

CRAVIT® I.V. are indicated for the treatment of adults (≥18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below. CRAVIT® I.V. is indicated when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form). Please see **DOSAGE AND ADMINISTRATION** for specific recommendations.

Acute bacterial sinusitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.

Acute bacterial exacerbation of chronic bronchitis due to *Staphylococcus aureus*, *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* or *Moraxella catarrhalis*.

Community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin – resistant strains, MIC value for penicillin ≥ 2µg/mL), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae, Legionella pneumophila*, or *Mycoplasma pneumoniae*. (See **CLINICAL STUDIES**.)

Nosocomial pneumonia due to methicillin- susceptible *Staphylococcus aureus*, *Pseudomonas aeruginosa, Seratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae*, or *Streptococcus pneumoniae.* Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

Complicated skin and skin structure infections due to methicillin – sensitive *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes*, or *Proteus mirabilis.*

Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impertigo, pyoderma, wound infections due to *Staphylococcus aureus*, or *Streptococcus pyogenes.*

Complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae*, *Proteus mirabilis*, or *Pseudomonas aeruginosa.*

Acute pyelonephritis (mild to moderate) caused by *Escherichia coli*.

Uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus*

Chronic bacterial prostatitis due to *Escherichia coli, Enterococcus faecalis*, or methicillin – susceptible *Staphylococcus epidermidis*.

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. 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 strains of *Pseudomonas aeruginosa* may develop resistance fairly rapidly during treatment with levofloxacin. Culture and susceptibility testing performed periodically during therapy will provide information about the continued susceptibility of the pathogens to the antimicrobial agent and also the possible emergence of bacterial resistance.

CONTRAINDICATIONS

Levofloxacin is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

WARNINGS

THE SAFETY AND EFFICACY OF LEVOFLOXACIN INPEDIATRIC PATIENTS, ADOLESCENTS (UNDER THE AGE OF 18 YEARS), PREGNANT WOMEN, AND NURSING WOMEN HAVE NOT BEEN ESTABLISHED. (See **PRECAUTIONS: Pediatric Use, Pregnancy**, and **Nursing Mothers** subsections.)

In immature rats and dogs, the oral and intravenous administration of levofloxacin increased the incidence and severity of osteochondrosis. Other fluoroquinolones also produce similar erosions in the weight bearing joints and other signs of arthropathy in immature animals of various species. (See **ANIMAL PHARMACOLOGY.)**

Peripheral Neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesia, hypoesthesia, dysesthesias and weakness have been reported in patients receiving fluoroquinolones, including CRAVIT ® I.V.Symptoms may occur soon after initiation of CRAVIT® I.V. and may be irreversible. CRAVIT® I.V. should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness or other alteration of sensation including light touch, pain, temperature, position sense, and vibratory sensation.

Cardiac disorders

Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmic, tricyclic antidepressants, macrolides, antipsychotics)
- Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesaemia)
- Elderly
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilator support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid levofloxacin in patients with a known history of myasthenia gravis.

Convulsion and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation which may lead to tremors, restlessness, anxiety, lightheadedness, confusion, hallucinations, paranoia, depression, nightmares, insomnia, and rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction.)

(See **PRECAUTIONS: General, Information for Patients, Drug Interactions** and **ADVERSE REACTIONS**.)

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

Serious and sometimes fatal events, some due to hypersensitivity, and some due to uncertain etiology, have been reported rarely in patients receiving therapy with quinolones, including levofloxacin. These events may be severe and generally occur following the administration of multiple doses. Clinical manifestation may include one or more of the following: fever, rash or severe dermatologic reactions (e.g., toxic epidermal necrolysis, Stevens-Johnson Syndrome); vasculitis; arthralgia; myalgia; serum sickness; allergic pneumonitis; interstitial nephritis; acute renal insufficiency or failure; hepatitis; jaundice; acute hepatic necrosis or failure; anemia including hemolytic and aplastic; thrombocytopenia, including thrombotic thrombocytopenic purpura; leukopenia; agranulocytosis; pancytopenia; and/or other hematologic abnormalities. The drug should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity and supportive measures instituted. (See **PRECAUTIONS: Information for Patients** and **ADVERSE REACTIONS.)**

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of “antibiotic-associated colitis.”

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes,

protein supplementation, and treatment with an antibacterial drug clinically effective against C. *difficile* colitis. (See **ADVERSE REACTIONS.)**

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Post-marketing surveillance reports indicate that this risk may be increased in patients receiving concomitant corticosteroids, especially in the elderly. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

Disabling and potentially irreversible serious adverse reactions
Fluoroquinolones, including CRAVIT I.V. have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue CRAVIT I.V. immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including CRAVIT I.V. in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Aortic aneurysm or dissection and heart valve regurgitation/incompetence
Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in the older population, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, heart valve disease, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behçet´s disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities

Psychiatric Adverse Reactions
Fluoroquinolones, including CRAVIT I.V. have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving CRAVIT I.V. discontinue CRAVIT I.V. immediately and institute appropriate measures.

Blood Glucose Disturbances
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with [Product Name]. In [Product Name]-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (for example, sulfonylurea) or with insulin. Severe cases of hypoglycemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs, discontinue CRAVIT I.V. and initiate appropriate therapy immediately.

PRECAUTIONS

General

Because a rapid or bolus intravenous injection may result in hypertension, LEVOFLOXACIN INJECTION SHOULD ONLY BE ADMINISTERED BY SLOW INTRAVENOUS INFUSION OVER A PERIOD OF 60 OR 90 MINUTES DEPENDING ON THE DOSAGE. (See **DOSAGE AND ADMINISTRATION**.)

Although levofloxacin is more solution than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

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. 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 **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINITRATION**.)

Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. However, in clinical trials with levofloxacin, phototoxicity has been observed in less than 0.1% of patients. Therapy should be discontinued if phototoxicity (e.g., a skin eruption) occurs.

As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). (See **WARNINGS** and **Drug Interactions**.)

As with other quinolones, disturbances of blood glucose, including symptomatic hyper-and hypoglycemia, have been reported, usually in diabetic patients receiving concomitant treatment with an oral

hypoglycemic agent (e.g., glyburide/glibenclamide) 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 immediately and appropriate therapy should be initiated immediately. (See **Drug Interactions** and **ADVERSE REACTIONS.)**

Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval on the electrocardiogram (see **CLINICAL PHARMACOLOGY** : **Electrocardiogram**) and infrequent cases of arrhythmia. During post-marketing surveillance, very rare cases of torsades de pointes have been reported in patients taking levofloxacin. These reports generally involved patients with concurrent medical conditions or concomitant medications that may have been contributory. The risk of arrhythmias may be reduced by avoiding concurrent use with other drugs that prolong the QT interval including class la or class III antiarrhythmic agents; in addition, use of levofloxacin in the presence of risk factors for torsades de pointes such as hypokalemia, significant bradycardia, and cardiomyopathy should be avoided.

As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during therapy. (See **WARNINGS** and **ADVERSE REACTIONS**.)

Information for Patients

Patients should be advised:

- to drink fluids liberally:
- to inform their physician of any history of myasthenia gravis and to notify their physician if they experience any symptoms of muscle weakness, including respiratory difficulties
- that antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc or Videx ® (Didanosine), chewable/buffered tablets or the pediatric power for oral solution should be taken at least two hours before or two hours after oral levofloxacin administration. (See **Drug Interactions**);
- that oral levofloxacin can be taken without regard to meals;
- that levofloxacin may cause neurologic adverse effects (e.g., dizziness, lightheadedness) and that 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. (See **WARNINGS** and **ADVERSE REACTIONS**)
- to discontinue treatment and inform their physician if they experience pain, inflammation, or rupture of a tendon, and to rest and refrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded;
- that levofloxacin may be associated with hypersensitivity reactions, even following the first dose, and to discontinue the drug at the first sign of a skin rash, hives or other skin reaction, 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 of an allergic reaction. (See **WARNINGS** and **ADVERSE REACTIONS**);
- to avoid excessive sunlight or artificial ultraviolet light while receiving levofloxacin and to discontinue therapy if phototoxicity (i.e., skin eruption) occurs;
- 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. (See **PRECAUTIONS: General** and **Drug Interactions**.);

- that concurrent administration of warfarin and levofloxacin has been associated with increases of the International Normalized Ratio (INR) or prothrombin time and clinical episodes of bleeding. Patients should notify their physician if they are taking warfarin.
- That convulsions have been reported in patients taking quinolones, including levofloxacin, and to notify their physician before taking this drug if there is a history of this condition.

Drug Interactions
Drugs known to prolong QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmic, tricyclic antidepressants, macrolides, antipsychotics)

Antacids, Sucralfate, Metal Cations, Multivitamins
CRAVIT® I.V.: There are no data concerning an interaction of intravenous fluoroquinolone with oral antacids, Sucralfate, Metal Cations, Multivitamins, Videx (Didanosine) , or Metal cations. However, no quinolone should be co-administrated with any solution containing multivalent cations, e.g. magnesium, through the same intravenous line (See DOSAGE AND ADMINISTRATIVE)

Theophylline: No significant effect to levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline was detected in a clinical study involving 14 healthy volunteers. Similarly, no apparent effect to the theophylline on levofloxacin absorption and disposition was observed. However, concomitant administration of other quinolones with theophylline has resulted in prolonged elimination half-life, elevated serum theophylline levels, and a subsequent increase in the risk of theophylline-related adverse reactions in the patient population. Therefore, theophylline levels should be closely monitored and appropriate dosage adjustments made when levofloxacin is co-administered. Adverse reactions, including seizures, may occur with or without a deviation in serum theophylline levels (See DOSAGE AND ADMINISTRATIVE)

Warfarin: No significant effect to 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. There have been reports during the post marketing experience in patients that levofloxacin enhances the effects of warfarin. Elevations of prothrombin time in the setting of concurrent warfarin and levofloxacin use have been associated with episodes of bleeding. Prothrombin time, international Normalized Ration (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.

Cyclosporine: No significant effect of levofloxacin on the peak plasma concentrations, AUC, and other disposition parameters for cyclosporine was detected in a clinical study involving healthy volunteers. However, elevated serum levels of cyclosporine have been reported in the patient population when co-administered with some other quinolones. Levofloxacin Cmax and t1/2 were slightly lower while Tmax and T1/2 were slightly longer in the presence of cyclosporine than those observed in the 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.

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.

Probenecid and Cimetidine: No significant effect of Probenecid and Cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers. The AUC and t1/2 of levofloxacin were 27-38% and 30% higher, respectively. While CL/F and CLr were 21-35% lower during concomitant treatment with probenecid or cimetidine compared to levofloxacin alone. Although these differences were statistically significant, the changes were not high enough to warrant dosage adjustment for levofloxacin when probenecid or cimetidine is co-administered.

Non-Steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures. (See WARNING and PRECAUTIONS: General.)

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a lifetime bioassay in rats, levofloxacin exhibited no carcinogenic potential following daily dietary administration for 2 years; the highest dose (100 mg/kg/day) was 1.4 times he highest recommended human dose (750mg) based upon relative body surface area.

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (*S.typhumurium* 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.

Pregnancy: Teratogenic Effects. Pregnancy Category C

Levofloxacin was not teratogen in rats at oral doses as high as 810 mg/kg/day which corresponds to 9.4 times the highest recommended human dose based upon relative body surface area, or at intravenous doses as high as 160 mg/kg/day corresponding to 1.9 times the highest recommended human dose based upon relative body surface area. The oral dose of 810 mg/kg/day to rats caused decreased fetal body weight and increased fetal mortality. No teratogenicity was observed when rabbits were dosed orally as high as 50mg/kg/day which corresponds to 1.1 times the highest recommend 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 woman. Levofloxacin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. (See WARNINGS)

Nursing Mothers

Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients and adolescents below the age of 18 years have not been established. Quinolones, including levofloxacin, cause arthropathy and osteochondrosis in juvenile animals of several species. (See WARNING)

Geriatric Use

In phase 3 clinical trials, 1190 levofloxacin-treated patients (25%) were >= 65 years of age. Of these, 675 patients (14%) were between the ages of 65 and 74 and 515 (11%) were 75 years old or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experiences has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out

The pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly when creatinine clearance is taken into consideration. However since the drug is known to be substantially excreted by the kidney, the risk of toxic reactions to this drug may be greater in patients with renal 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.

Adverse reactions

The incidence of drug-related adverse reaction in patients during Phase3 clinical trials conducted in North America was 6.3%. Among patients receiving levofloxacin therapy, 3.9% discontinued levofloxacin therapy due to adverse experiences. The overall incidence, type and distribution of adverse events was similar in patients receiving levofloxacin doses of 750 mg once daily compared to patients receiving dose from 250 mg once daily to 500 mg once daily.

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin: nausea 1.3%, diarrhea 1.0%, vaginitis 0.7%, insomnia 0.5%, abdominal pain 0.4%, flatulence 0.4%, pruritus 0.4%, dizziness 0.3%, dyspepsia 0.3%, rash 0.3%, genital moniliasis 0.2%, taste perversion 0.2%, vomiting 0.2%, constipation 0.1%, fungal infection 0.1%, genital pruritus 0.1%, headache 0.1%, moniliasis 0.1%, nervousness 0.1%, rash erythematous 0.1, urticarial 0.1%

In clinical trials, the following events occurred in> 3% of patients, regardless of drug relationship: nausea 7.2%, headache 6.4%, diarrhea 5.6%, insomnia 4.6%, injection site reaction 3.5%, constipation 3.2%

In clinical trials, the following events occurred in 1 to 3% of patients regardless of drug relationship: dizziness 2.7%, abdominal pain 2.5%, dyspepsia 2.4%, vomiting 2.3%, vaginitis 1.8%, injection site pain 1.7%, flatulence 1.5%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain 1.2%, fatigue 1.2%, rash 1.2%, back pain 1.1%, injection site inflammation 1.1%, rhinitis 1.0%, taste perversion 1.0%

In clinical trials, the following events, of potential medical importance, occurred at a rate of less than 1.0%, regardless of drug relationship:

Autonomic Nervous system Disorder:	postural hypotension
Body as a whole – General Disorder:	asthenia, edema, fever, malaise, rigors, substernal chest pain, syncope
Cardiovascular Disorder, General:	cardiac failure, circulatory failure, hypertension, hypotension,
Central and Peripheral nervous system disorder:	abnormal coordination, coma, convulsions (seizures), hyperkinesia, hypertonia, hypoesthesia, involuntary muscle contraction, paresthesia, paralysis, speech disorder, stupor, tremor, vertigo
Gastro-Intestinal System Disorder:	dry mouth, dysphagia, gastroenteritis, GI hemorrhage pancreatitis, pseudomembranous colitis, tongue edema
Hearing and Vestibular Disorder:	ear disorder (not otherwise specified), tinnitus
Heart rate and Rhythm Disorder:	arrhythmia, atrial fibrillation, bradycardia, cardiac arrest, heart block, palpitation, supraventricular tachycardia, ventricular fibrillation
Liver and Biliary System Disorder:	abnormal hepatic function, cholelithiasis, hepatic coma, jaundice
Metabolic and Nutritional Disorder:	aggravated diabetes mellitus, dehydration, hyperglycemia, hyperkalemia, hypoglycemia, hypokalemia, increased LDH, weight decrease
Musculo-Skeleton System Disorder:	arthralgia, arthritis, arthrosis, muscle weakness, myalgia, osteomyelitis, rhabdomyolysis, synovitis, tendinitis
Myo, Endo, Pericardial and Valve Disorder:	angina pectoris, coronary thrombosis, myocardial infraction
Neroplasms:	Carcinoma
Other Special Senses Disorders:	Parosmia
Platelet, Bleeding and Clotting Disorders:	Abnormal platelets, embolism(blood clot), epistaxis, purpura, thrombocytopenia
Psychiatric Disorders:	Abnormal dreaming, aggressive reaction, agitation, anorexia, anxiety, confusion, delirium, depression, emotional liability, hallucination, impaired concentration, impotence, manic reaction, mental deficiency, nervousness, paranoia, sleep disorder, somnolence, withdrawal syndrome
Red Blood Cell Disorders:	Anemia
Reproductive Disorders:	Ejaculation failure
Resistance Mechanism Disorder:	Fungal infection, genital moniliasis
Respiratory System Disorders:	ADRS, asthma, coughing, dyspnea, haemoptysis, hypoxia, pleural effusion, respiratory insufficiency
Skin and Appendages Disorders:	Erythema nodosum, genital pruritus, increased sweating, skin disorder, skin exfoliation, skin ulceration, urticarial
Urinary System Disorders:	Abnormal renal function, acute renal failure, face edema, haematuria
Vascular (Extracardiac) Disorders:	Cerebrovascular disorder, phlebitis
Vision Disorders:	Abnormal vision, conjunctivitis, diplopia

White cell and RES Disorders:	Granulocytopenia, leukocytosis, leukopenia, lymphadenopathy, WBC abnormal (not otherwise specified)

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

Heart Rate and Rhythm Disorders

Not known : ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECGQT prolonged

Crystalluria and cylindruria have been reported with other quinolones.

The following laboratory abnormalities appeared in 2.2% of patients receiving levofloxacin. It is not known whether these abnormalities were caused by the drug or the underlying condition being treated.

Blood chemistry: decreased glucose
Hematology: decreased lymphocytes

Post-Marketing Adverse Reactions

Additional adverse events reported from worldwide post-marketing experience with levofloxacin include: allergic pneumonitis anaphylactic shock, anaphylactoid reaction, dysphonia, abnormal EEG, encephalopathy, eosinophilia, erythema multiforme, hemolytic anemia, multi-system organ failure, increased International Normalized Ratio(INR)/ prothrombin time, Stevens- Johnson Syndrome, tendon rupture, tosades de pointes, vasodilation. Exacerbation of myasthenia gravis. Nervous system disorders (frequency not known): Peripheral neuropathy (that may be irreversible) and polyneuropathy

OVERDOSAGE

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

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

DOSAGE AND ADMINISTRATION

CRAVIT ® I.V. should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitioneal, or subcutaneous administration.

CAUTION: RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED. Levofloxacin Injection should be infused intravenously slowly over a period of not less than 60 or 90 minutes, depending on the dosage. (See **PRECAUTIONS.)**

The usual dose of CRAVIT ® I.V. is 250 mg or 500 mg administered orally or by slow infusion over 60 minutes every 24 hours or 750 mg administered by slow infusion over 90 minutes every 24 hours, as indicated by infection and described in the following dosing chart. These recommendations apply to patients with normal renal function (i.e., creatinine clearance >80 mL/min). For patients with altered renal function see the **Patients with Impaired Renal Function** subsection.

Patients with Normal Renal Function

Infection*	Unit Dose	Freq.	Duration**	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Community-Acquired Pneumonia	500 mg	q24h	7-14 days	500 mg
Nosocomial Pneumonia	750 mg	q24h	7-14 days	750 mg
Acute Bacterial Sinusitis	500 mg	q24h	10-14 days	500 mg
Complicated SSSI	750 mg	q24h	7-14 days	750 mg
Uncomplicated SSSI	500 mg	q24h	7-10 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg
Chronic Bacterial Prostatitis	500 mg	q24h	28 days	500 mg

*__DUE TO THE DESIGNATED PATHOGENS__ (See __INDICATIONS AND USAGE__.)

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

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis/		
Comm. Acquired Pneumonia/ Acute Maxillary Sinusitis/ Uncomplicated SSSI		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	500 mg	250 mg q24h
CL_{CR} from 10 to 19 mL/min	500 mg	250 mg q48h
Hemodialysis	500 mg	250 mg q48h
CAPD	500 mg	250 mg q48h
Complicated SSSI		
CL_{CR} from 50 to 80 mL/min	No dosage adjustment required	
CL_{CR} from 20 to 49 mL/min	750 mg	750 mg q48h
CL_{CR} from 10 to 19 mL/min	750 mg	500 mg q48h
Hemodialysis	750 mg	500 mg q48h
CAPD	750 mg	500 mg q48h
Complicated UTI/ Acute Pyelonephritis		
CL_{CR} ≥20 mL/min	No dosage adjustment required	
CL_{CR} from 10 to 19 mL/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{CR} = Creatinine clearances

CAPD = chronic ambulatory peritoneal dialysis

When only the serum creatinine is known, the following formula may be used to estimate creatinine clearance.

Men: Creatinine Clearance (mL/min) = $\frac{\text{Weight (kg) x (140 – age)}}{\text{72 x serum creatinine (mg/dL)}}$

Women: 0.85 x the value calculated for men.

The serum creatinine should represent a steady state of renal function.

Stability of CRAVIT ® I.V. as Supplied

When stored under recommended conditions, CRAVIT ® I.V., as supplied in 50 mL and 100 mL vials, is stable through the expiration date printed on the label.

COMPATABILITIES/ INCOMPATABILITIES INFORMATION

Since CRAVIT® I.V. 5 mg/mL is ready for use, it may be given alone or with one of the following solutions.

0.9% sodium chloride solution, 5% dextrose injection, 2.5% dextrose in Ringer solution and combination solutions for parenteral nutrition (amino acids, carbonhydrates, electrolytes).

CRAVIT ® I.V.solution for infusion should not be mixed with certain other solutions (e.g., sodium hydrogen carbonate) or with heparin.

PRESENTATION AND STORAGE

CRAVIT® I.V.5 mg/mL solution for infusion is supplied as a clear, ready to use 50 mL and 100 mL solution in glass bottle. Store at or below 30 °C in well-closed container and protect from light.

CLINICAL STUDIES

Community- Acquired Bacterial Pneumonia

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia were evaluated in two pivotal clinical studies In the first study, 590 patients were enrolled in 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 inrolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days posttherapy, and 3 to 4 weeks posttherapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days posttherapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%) . [95% Cl of -19, -6]. In the second study, 264 patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96% and 96% and 70%, respectively.

Microbiologic eradication rates across both studies were as follows:

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

Additional studies were initiated to evaluate the utility of CRAVIT in community – acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin – resistant strains (MIC value for penicillin ≥ 2 µg/mL)

In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were evaluated in six additional clinical studies; one double-blind study, two open label randomized studies, and threeopen label non-comparative studies. The total number of clinically evaluable patients with S.*pneumoniae* across all 8 studies was 250 for levofloxacin and 41 for comparators. The clinical success rate (cured or improved) among the 250 levofloxacin-treated patients with S.*pneumoniae* was 245/250 (98%). The clinical success rate among the 41 comparator- treated patients with S.*pneumoniae* was 39/41 (95%).

Across these 8 studies, 18 levofloxacin-treated and 4 non-quinolone comparator-treated patients with community-acquired pneumonia due to penicillin- resistant S.*pneumoniae* (MIC value for penicillin ≥ 2 µg/mL) were identified. Of the 18 levofloxacin-treated patients, 15 were evaluable following the completion of therapy. Fifteen out of the 15 evaluable levofloxacin – treated patients with community-acquired pneumonia due to penicillin-resistant S.*pneumoniae* achieved clinical success (cure or improvement). Of these 15 patients, 6 were bacteremic and 5 were classified as having severe disease. Of the 4 comparator-treated patients with community- acquired pneumonia due to penicillin – resistant S.*pneumoniae*, 3 were evaluable for clinical efficacy. Three out of the 3 evaluable comparator- treated patients achieved clinical success. All three of the comparator – treated patients were bacteremic and had disease classified as severe.

Nosocomial pneumonia

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

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

to the treatment regimen of 37 of 93 (39.8%) patients in the levofloxacin arm and 28 of 94 (29.8%) patients in the comparator arm for suspected methicillin – resistant S.*aureus* infection.

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

Clinical success rates and microbiological eradication rates (Nosocomial Pneumonia)

Pathogen	**N**	**CRAVIT 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[1]	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[2]	11	9 (81.8)/ 5 (45.5)	7	6 (85.7)/ 3 (42.9)
H.*influenzae*	16	13 (81.3)/ 10 (62.5)	15	14 (93.3)/11 (73.3)
S.*pneumoniae*	4	3 (75.0)/3 (75.0)	7	5 (71.4)/4 (57.1)

*Methicillin – susceptible *S. aureus*

[1] See above text for use of combination therapy

[2] The observed differences in rates for the clinical and microbiological outcomes may reflect other factors that were not accounted for in the study

Complicated Skin And Skin Structure Infections

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

Among those who could be evaluated clinically 2-5 days after completion of study drug, overall success rates (improved or cured) were 116/138 (84.1%) for patients treated with levofloxacin and 106/132 (80.3%) for patients treated with the comparator.

Success rates varied with the type of diagnosis ranging from 68% in patients with infected ulcers to 90% in patients with infected wounds and abscesses. These rates were equivalent to those seen with comparator drugs.

Chronic Bacterial Prostatitis

Adult patients with a clinical diagnosis of prostatitis and microbiological culture results from urine sample collected after prostatic massage (VB_3) or expressed prostatic secretion (EPS) specimens obtained via the Meares-Stamey procedure were enrolled in a multicenter, randomized, double-blind study comparing oral levofloxacin 500 mg, once daily for a total of 28 days to oral ciprofloxacin 500 mg, twice daily for a total of 28 days. The primary efficacy endpoint was microbiologic efficacy in microbiologically evaluable patients. A total of 136 and 125 microbiologically evaluable patients were enrolled in the levofloxacin and ciprofloxacin groups, respectively. The microbiologic eradication rate by patient infection at 5-18 days after completion of therapy was 75.0 % in the levofloxacin group and 76.8% in the ciprofloxacin group (95% Cl [-12.58, 8.98] for levofloxacin minus ciprofloxacin). The overall eradication rates for pathogens of interest are presented below.

Microbiological eradication rates (Chronic Bacterial Prostatitis)

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

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

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

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

ANIMAL PHARMACOLOGY

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. (See **WARNINGS**.)

In immature dogs (4-5 months old), oral doses of 10 mg/kg/day for 7 days and intravenous doses of 4 mg/kg/day for 14 days of levofloxacin resulted in arthropathic lesions. Administration at oral doses of 300 mg/kg/day for 7 days and intravenous doses of 60 mg/kg/day for 4 weeks produced arthropathy in juvenile rats.

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

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

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

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

In vitro and in vivo studies in animals indicate that levofloxacin is neither an enzyme inducer or inhibitor in the human therapeutic plasma concentration range; therefore, no drug metabolizing enzyme-related interactions with other drugs or agents are anticipated.

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