

MONOFLOX (levofloxacin) TABLETS

Monoflox (levofloxacin) is a synthetic broad-spectrum antibacterial agent for oral and intravenous administration.

Composition:

Each Monoflox [250-500-750] tablet contains Levofloxacin 250mg/500mg/700mg respectively.

CLINICAL PHARMACOLOGY

The mean \pm SD pharmacokinetic parameters of levofloxacin determined under single and steady-state conditions following oral (p.o.) tablet, oral solution, or intravenous (i.v.) doses of levofloxacin are summarized in Table I.

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.
- Levofloxacin pharmacokinetics is linear and predictable after single and multiple oral dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg or 750 mg once-daily dosage regimen.
- The mean \pm 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 $\mu\text{g/mL}$ after the 500 mg doses, and 8.6 ± 1.9 and 1.1 ± 0.4 $\mu\text{g/mL}$ after the 750 mg doses, respectively.
- Oral administration of 500 mg LEVAQUIN with food prolongs the time to peak concentration by approximately 1 hour & decreases the peak concentration by around 14%.

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 administrations 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 $\mu\text{g/g}$ over a 24-hour period after a single 500 mg oral dose.
- In vitro, over a clinically relevant range (1 to 10 $\mu\text{g/mL}$) 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 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.

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: half-life –

- 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.
- 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.

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.

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.

Table 1. Mean ±SD Levofloxacin PK Parameters

Regimen	C _{max} (µg/mL)	T _{max} (h)	AUC (µg·h/mL)	t _{1/2} (h)	CLR (mL/min)
250mg	2.8 ± 0.4	1.6 ± 1.0	27.2 ± 3.9	7.3 ± 0.9	142 ± 21
500mg	5.1 ± 0.8	1.3 ± 0.6	47.9 ± 6.8	6.3 ± 0.6	103 ± 30
750mg	9.3 ± 1.6	1.6 ± 0.8	101 ± 20	7.5 ± 0.9	ND
500mg single dose: effects of gender and age					
Male	5.5 ± 1.1	1.2 ± 0.4	54.4 ± 18.9	7.5 ± 2.1	126 ± 38
Female	7.0 ± 1.6	1.7 ± 0.5	67.7 ± 24.2	6.1 ± 0.8	106 ± 40
Elderly	7.0 ± 1.6	1.4 ± 0.5	74.7 ± 23.3	7.6 ± 2.0	91 ± 29
Young	5.5 ± 1.0	1.5 ± 0.6	47.5 ± 9.8	6.0 ± 0.9	140 ± 33
500mg single dose: patients with renal insufficiency					
CL_{CR} 50-80mL/min	7.5 ± 1.8	1.5 ± 0.5	95.6 ± 11.8	9.1 ± 0.9	57 ± 8
CL_{CR} 20-49mL/min	7.1 ± 3.1	2.1 ± 1.3	182.1 ± 62.6	27 ± 10	26 ± 13
CL_{CR} <20mL/min	8.2 ± 2.6	1.1 ± 1.0	263.5 ± 72.5	35 ± 5	13 ± 3
Hemodialysis	5.7 ± 1.0	2.8 ± 2.2	ND	13 ± 3	ND
CAPD	6.9 ± 2.3	1.4 ± 1.1	ND	51 ± 24	ND

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 topoisomerase), 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 penicillins. Fluoroquinolones may, therefore, be active against bacteria resistant to these antimicrobials.

Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence (range: 10^{-9} to 10^{-10}). 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 (many strains are only moderately susceptible)
- ☐ Staphylococcus aureus (methicillin-susceptible strains)
- ☐ Staphylococcus epidermidis (methicillin-susceptible strains)
- ☐ Staphylococcus saprophyticus
- ☐ Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]*)
- ☐ Streptococcus pyogenes
- ☐ *MDRSP (Multi-drug resistant Streptococcus pneumoniae)

Aerobic gram-negative microorganisms

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

Other microorganisms

- ☐ Chlamydia pneumoniae
- ☐ Mycoplasma pneumoniae
- ☐ Levofloxacin has been shown to be active against Bacillus anthracis both in vitro and by use of plasma levels as a surrogate marker in a rhesus monkey model for anthrax (post-exposure).

The following in vitro data are available, **but their clinical significance is unknown.**

- ☐ Levofloxacin exhibits in vitro minimum inhibitory concentrations (MIC values) of 2 μ g/mL or less against most ($\geq 90\%$) 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 microorganisms

- ☐ Staphylococcus haemolyticus
- ☐ Streptococcus (Group G)
- ☐ Streptococcus milleri
- ☐ Streptococcus (Group C/F)
- ☐ Streptococcus agalactiae
- ☐ Viridans group streptococci

Aerobic gram-negative microorganisms

- ☐ Acinetobacter baumannii

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

Anaerobic gram-positive microorganisms

- ☐ Clostridium perfringens

MIC₉₀ values:

Standard levofloxacin powder should give the following MIC values:

No	Bacteria	MIC ₉₀ (µg/mL)
1	Enterococcus faecalis	0.25-2
2	Escherichia coli	0.008-0.06
3	Haemophilus influenzae	0.008-0.03
4	Pseudomonas aeruginosa	0.5-4
5	Staphylococcus aureus	0.06-0.5
6	Streptococcus pneumoniae	0.5-2

INDICATIONS AND USAGE

Monoflox Tablets 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.

- ☐ **Acute bacterial sinusitis**
- ☐ **Acute bacterial exacerbation of chronic bronchitis**
- ☐ **Nosocomial pneumonia**
- ☐ **Community-acquired pneumonia**
- ☐ **Complicated skin and skin structure infections**
- ☐ **Uncomplicated skin and skin structure infections**
- ☐ **Chronic bacterial prostatitis**
- ☐ **Complicated urinary tract infections**
- ☐ **Acute pyelonephritis**
- ☐ **Uncomplicated urinary tract infections**
- ☐ **Inhalational anthrax (post-exposure)**

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 in pediatric patients, adolescents (under the age of 18 years), pregnant women, and nursing women have not been established.
- ☐ 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.
- ☐ Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity.

- **Peripheral Neuropathy:** Rare 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 quinolones, including levofloxacin.
- **Tendon Effects:** Ruptures of the shoulder, hand, Achilles tendon, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin.

Drug Interactions

- **Antacids, Sucralfate, Metal Cations, Multivitamins** may interfere with the gastrointestinal absorption of levofloxacin, resulting in systemic levels considerably lower than desired. These agents should be taken at least two hours before or two hours after levofloxacin administration.
- **Theophylline:** No significant effect of levofloxacin pharmacokinetics, 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.
- **Warfarin:** No significant effect of levofloxacin pharmacokinetics. But 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.
- **Cyclosporine:** No significant effect of levofloxacin pharmacokinetics. But elevated serum levels of cyclosporine have been reported when co-administered with some other quinolones
- **Digoxin:** No significant effect of levofloxacin pharmacokinetics.
- **Probenecid and Cimetidine:** No significant effect of levofloxacin pharmacokinetics.
- **NSAIDs:** The concomitant administration of a non-steroidal anti-inflammatory drug with levofloxacin may increase the risk of CNS stimulation and convulsive seizures.
- **Antidiabetic agents:** Disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent.

Precautions:

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.
- 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.

Nursing Mothers

- Levofloxacin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin may be excreted in human milk. Hence, levofloxacin should be used if most necessary.

Pediatric Use

Safety and effectiveness in pediatric patients and adolescents < age of 18 years have not been established.

Geriatric Use

Elderly patients may be more susceptible to drug-associated effects on the QT interval. Therefore, precaution should be taken when using levofloxacin with concomitant drugs that can result in prolongation of the QT interval (e.g. class IA or class III antiarrhythmics) or in patients with risk factors for Torsades de pointes (e.g. known QT prolongation, uncorrected hypokalemia).

ADVERSE REACTIONS

In clinical trials, the following events were considered likely to be drug-related in patients receiving levofloxacin: Nausea 1.5%, Diarrhea 1.2%, Vaginitis 0.5%, Insomnia 0.4%, Abdominal pain 0.4%, Flatulence 0.2%, Pruritus 0.2%, Dizziness 0.3%, rash 0.3%, dyspepsia 0.3%, genital moniliasis 0.1%, moniliasis 0.2%, taste perversion 0.2%, vomiting 0.3%.

OVERDOSAGE

Levofloxacin exhibits a low potential for acute toxicity.

DOSAGE AND ADMINISTRATION of MONOFLOX tablets

Patients with Normal Renal Function

Infection	Unit dose [mg]	Frequency	Duration [days]	Daily dose [mg]
CAP	500	OD	7-14	500

CAP	750	OD	5	750
Nosocomial pneumonia	750	OD	7-14	750
Acute Bacterial sinusitis	500	OD	10-14	500
Acute Bacterial sinusitis	750	OD	5	750
Complicated SSSI	750	OD	7-14	750
AECB	500	OD	7	500
Uncomplicated SSSI	500	OD	7-10	500
Chr. Bacterial Prostatitis	500	OD	28	500
Complicated UTI	250	OD	10	250
Acute pyelonephritis	250	OD	10	250
Uncomplicated UTI	250	OD	3	250

Patients with Impaired Renal Function

Renal Status	Initial dose [mg]	Subsequent Dose [mg]	Frequency
AECB, CAP, Acute Bacterial Sinusitis, Uncomplicated SSSI, Chr, bacterial Prostitis, Inhalation Anthrax			
CL _{CR} From 50-80mL/min	No Dose adjustment required		
CL _{CR} From 20-49mL/min	500	250	OD/24h
CL _{CR} From 10-19mL/min	500	250	OD/48h
Hemodialysis	500	250	OD/48h
CAPD	500	250	OD/48h
Complicated SSSI, Nosocomial pneumonia, CAP, Acute Bacterial Sinusitis			
CL _{CR} From 50-80mL/min	No Dose adjustment required		
CL _{CR} From 20-49mL/min	750	750	OD/48h
CL _{CR} From 10-19mL/min	750	500	OD/48h
Hemodialysis	750	500	OD/48h
CAPD	750	500	OD/48h
Complicated UTI/ acute Pyelonephritis			
CL _{CR} From ≥20mL/min	No Dose adjustment required		
CL _{CR} From 10-19mL/min	250	250	OD/48h
Uncomplicated UTI	No Dose adjustment required		