Levox™

Levofloxacin Infusion I. V.

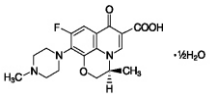
COMPOSITION
Each 100 ml contains:

Levofloxacin Hemihydrate equivalent to Levofloxacin	500 mg
Water for Injections BP	q.s.

Levox™ is a sterile, preservative-free, aqueous solution of Levofloxacin. The appearance of Levofloxacin injection may range from a clear yellow to greenish yellow solution.

DESCRIPTION : Levofloxacin (active ingredient)
Levofloxacin is a synthetic broad-spectrum antibacterial agent for IV/oral administration. Chemically, Levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance Ofloxacin. The chemical name is (-)-(S)-9-fluoro-2, 3 dihydro-3-methyl-10-(4-methyl-1-piper-azinyl)-7-oxo-7H-pyrido[1,2,3de]-1,4-benzoxazine-6-carboxylic acid hemihydrate. Its empirical formula is $C_{18}H_{20}FN_3O_4$ 1/2H_2O and its molecular weight is 370.38

Levofloxacin Structural Formula:



PHARMACODYNAMIC PROPERTIES
Levofloxacin is the L-isomer of the racemate, Ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of Ofloxacin resides primarily in the L-isomer.

MODE OF ACTION
The mechanism of action of levofloxacin and other fluoroquinolone antimicrobial involves inhibition of DNA gyrase (bacterial topoisomerase II) enzyme required for DNA replication, transcription, repair and recombination.

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 section.

BREAKPOINTS
The preliminary NCCLS (US National Committee on Clinical Laboratory Standards) recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are (Susceptible < 2 mcg/ml, resistant > 8 mcg/ml)

ANTIBACTERIAL SPECTRUM
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Therefore, the information presented provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to levofloxacin or not. Only microorganisms relevant to the given clinical indications are presented here.

AEROBIC GRAM- POSITIVE MICROORGANISMS
Enterococcus faecalis (many strains are only moderately susceptible) Staphylococus aureus (methicillin susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (Including penicillin Resistant Strains)
Streptococcus pyogenes

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 pneumoniae
Mycoplasma pneumoniae

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

Levofloxacin exhibits in vitro minimum inhibitory concentrations (MICs) of 2 µg/ ml or less against most 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 epidermidis (Methicillin susceptible strains)
Streptococcus (Group C/ F)
Streptococcus (Group G)
Streptococcus agalactiae
Viridans group streptococci

AEROBIC GRAM-NEGATIVE MICROORGANISMS
Acinetobacter baumannii
Acinetobacter calcoaceticus
Acinetobacter lwoffii
Bordetell apertussis
Citrobacter diversus
Citrobacter freundii
Enterobacter aerogenes
Enterobacter agglomerans
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Pseudomonas fluorescens
Serratia marcescens
Enterobacter sakazakii

ANAEROBIC GRAM-POSITIVE MICROORGANISMS
Clostridium perfringens

PHARMACOKINETIC PROPERTIES
Absorption : Levofloxacin pharmacokinetics is linear over a range of 50 to 600 mg and predictable after single and multiple IV and oral dosing regimens. Steady state is reached within 48 hours following a 500-mg once-daily regimen. The peak and trough plasma concentrations attained following multiple once daily IV 500-mg regimens were approximately 6.4 and 0.6 µg/ml respectively.

Distribution : Approximately 30-40% of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation of levofloxacin after doses of 500mg twice daily. Steady state is achieved within 3 days.

Penetration into tissues and body fluids : Penetration into Bronchial Mucosa, Epithelial lining fluid (ELF) Maximum levofloxacin concentrations in bronchial mucosa and Epithelial lining fluid after 500 mg PO where 8.3 mcg per ml and 10.8 mcg per ml respectively. These were reached approx. 1 hour after administration.

Penetration into lung tissues : Maximum levofloxacin concentration in lung tissue after 500 mg PO were approximately 11.3 mcg/ml and were reached between 4 to 6 hours after administration. The concentration in the lungs consistently exceeded those in plasma.

Penetration into blister fluid : Maximum levofloxacin concentration of about 4 to 6.7 mcg per ml in the blister fluid were reached 2-4 hours after administration following 3 days treatment at 500 mg once or twice daily respectively.
Penetration into cerebrospinal fluid Levofloxacin has poor penetration into cerebrospinal fluid.
Concentration in urine. The mean concentrations 8-12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91/L and 200 mg/L respectively.

Metabolism : Levofloxacin is metabolised to a very small extent , the metabolites being desmethyl levofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination: Following oral and intravenous administration, levofloxacin is eliminated relatively slowly from the plasma

($t_{1/2}$ = 6-8 hrs) and the excretion is primarily by renal route (>85% of the administered dose). The mean apparent total body clearance and renal clearance range from approximately 144 to 226 ml/min and 96 to142 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. There are no major differences in the pharmacokinetics of levofloxacin following oral and intravenous administration.

SPECIAL POPULATIONS

Elderly subjects : There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences : Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics.There is no evidence that these gender differences are of clinical relevance.

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

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

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.

Renal insufficiency : The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function, renal elimination and clearance are decreased and elimination half lives increased as shown in the table below:

CL_{cr} (ml/min)	< 20	20-40	50-80
CL_r (ml/min)	13	26	57
$T_{1/2}$ (hrs)	35	27	9

Drug-drug interactions

(**See PRECAUTIONS**: Drug Interactions.)

INDICATIONS

Levox™ is 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 maxillary sinusitis due to *Streptococcus pneumoni 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, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella Catarrhalis, Chlamydia pneumoniae, Legionella pneumophila, or Mycoplasma pneumoniae.* **(See CLINICAL STUDIES.)**
- Uncomplicated skin and skin structure infections (mild to *moderate) including abscesses, cellulites, furuncles, impetigo, 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 *E. Coli, Klebsiella pneumoniae or Staphylococcus saprophyticus.*

DOSAGE AND ADMINISTRATION

Levofloxacin injection should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

CAUTION

RAPID OR BOLUS INTRAVENOUS INFUSION MUST BE AVOIDED.

Levox™ should be infused intravenously slowly over a period of not less than sixty minutes.

DURATION OF TREATMENT

The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general administration of **Levox**™ should be continued for a minimum of 48 to 72 hours after the patient has become febrile or evidence of bacterial eradication has been obtained.

The usual dose of **Levox**™ is 500 mg administered by slow infusion over 60 minutes every 24 hours as prescribed in the following dosing chart.

Patients with normal renal function: (i.e. creatinine clearance > 80 ml/ min)

Infection	Frequency	Duration	Daily Dose
Acute bacterial			
Exacerbation of			
chronic bronchitis	Once daily	7 days	500 mg
Community acquired	Once daily	7-14 days	500 mg
Pneumonia			
Acute maxillary			
sinusitis	Once daily	10-14 days	500 mg
Uncomplicated SSSI	Once daily	7-10 days	500 mg
Complicated UTI	Once daily	10 days	250 mg
Acute pyelonephritis	Once daily	10 days	250 mg
Uncomplicated UTI	Once daily	3 days	250 mg

Patients with impaired renal function:
(i.e. creatinine clearance < 80 ml/ min)

Acute bacterial Exacerbation of chronic bronchitis/ Community acquired pneumonia/ Acute maxillary sinusitis/ Uncomplicated SSSI

Renal status	Initial Dose	Subsequent Dose
CL_{CR} 50-80 ml/min.	No dosage	adjustment required
CL_{CR} 20-49 ml/min.	500 mg	250 mg once daily
CL_{CR} 10-19 ml/min.	500 mg	250 mg once in two days
Hemodialysis	500 mg	250 mg once in two days
CAPD	500 mg	250 mg once in two days

Complicated UTI / Acute Pyelonephritis

CL_{CR} 20 ml/min	No dosage	adjustment required
CL_{CR} from 10-19 ml/min	250 mg	250 mg q48h

CL_{CR}: Creatinine clearances

CAPD : Continuous ambulatory peritoneal dialysis

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

Men : Creatinine Clearance (ml/min) = [weight (kg) x (140-age)] / [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.

No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

CONTRA-INDICATIONS

LevoxinTM for infusion must not be used:

- In patients hypersensitive to levofloxacin, other quinolones and any of the excipients.
- in patients with epilepsy.
- In patients with history of tendon disorders related to fluoroquinolone administration.
- in children or growing aldolescents. (Under the age of 18 years)
- During pregancy.
- In breast-feeding women.

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 diarrhoea after the administration of any antibacterial agent.

CLOSTRIDIUM DIFFICLE- ASSOCIATED DISEASE

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin solution for infusion, may be symptomatic of Clostridium difficile associated disease, the most

severe form of which is pseudomembraneous colitis. If pseudomembraneous colitis is suspected, Levofloxacin solution for infusion must be stopped immediately and patient should be treated with supportive measures specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

In the most severe cases of pneumococcal pneumonia **Levox**™ may not be the optimal therapy.

Nosocomial infections due to P. aeruginosa may require combination therapy.

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

INFUSION TIME

The recommended infusion time of at least 60 minutes for 500 mg **Levox**™ for infusion should be observed. It is known for ofloxacin that during infusion tachychardia and temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, the infusion must be halted immediately.

TENDINITIS

Tendinitis, rarely observed with quinolones, may occassionaly lead to rupture, involving Achilles tendon in particular. Elderly patients are more prone to Tendinitis. The risk of tendon rupture may be increased by co-administration of corticosteroids. If tendinitis is suspected, treatment with **Levox**™ solution for infusion must be halted immediately and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

PATIENTS PREDISPOSED TO SEIZURES

Levox™ solution for infusion is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, such as patients with preexisting central nervous system lesions, concomitant treatment with fenbufen and similar non steroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold such as Theophylline.

PATIENTS WITH G-6- PHOSPHATE DEHYDROGENATED DEFICIENCY

Patients with latent or actual defects in glucose-6- phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents and so levofloxacin should be used with caution.

PATIENTS WITH RENAL IMPAIRMENT

Since levofloxacin is excreted mainly by the kidneys the dose of **Levox**™ should be adjusted in patients with renal impairment.

PREVENTION OF PHOTOSENSITISATION

Although Photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays in order to prevent Photosensitisation.

INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION:

Theophylline, fenbufen or similar nonsteroidal anti-inflammatory drugs

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study.

However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, NSAIDS or other agents, which lower the seizure threshold. Levofloxacin concentrations were about 13 % higher in the presence of fenbrufen than when administered alone. 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.

WARFARIN

No significant effect of levofloxacin on warfarin was detected in a clinical study involving healthy volunteers. No significant change in prothrombin time was noted in the presence of levofloxacin.

PROBENECID AND CIMETIDINE

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine 24% and probenecid 34%. This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is co administered with drugs that affect the tubular renal secretion such as probenecid and cimetidine specially in renally impaired patients.

CYCLOSPORIN

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 Tmax and 1½ were slightly longer in the presence of cyclosporine than those observed in other studies without concomitant medication. The differences, however, are not considered 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.

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.

USE DURING PREGNANCY AND LACTATION

Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight bearing cartilage of the growing organism, **Levox**™ must not be used in pregnant women.

LACTATION

In the absence of human data due to the experimental risk of damage by fluoroquinolones to the weight bearing cartilage of the growing organism, **Levox**™ solution for infusion must not be used in breast-feeding women.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Some undesirable effects may impair the patient's ability to concentrate and react and therefore may constitute a risk in situations where these abilities are of special importance

ADVERSE REACTIONS

The incidence of drug-related adverse reactions in patients during Phase 2 and 3 clinical trials conducted in North America was 6.2%. Among patients receiving multiple-dose therapy, 3.7% discontinued therapy with levofloxacin due to adverse experiences.

In clinical trials, the following events were considered likely to be drug-related in patients receiving multiple doses of levofloxacin: diarrhoea 1.1%, nausea 1.3%, vaginitis 0.7%, flatulence 0.4%, pruritus 0.5%, rash 0.3%, abdominal pain 0.4%, genital moniliasis 0.3%, dizziness 0.4%, dyspepsia 0.3%, insomnia 0.3%, taste perversion 0.2%, vomiting 0.2%, anorexia 0.1%, anxiety 0.1%, constipation 0.1%, edema 0.1%, fatigue 0.1%, headache 0.1%, increased sweating 0.1%, leukorrhea 0.1%, malaise 0.1%, nervousness 0.1%, sleep disorders 0.1%, tremor 0.1%, urticaria 0.1%.

In clinical trials, the most frequently reported adverse events occurring >3% of the study population regardless of drug relationship were: nausea 7.1%, diarrhoea 5.6%, headache 6.4%, injection site reaction 5.6%, insomnia 4.0%.

In clinical trials, the following events occurred in 1 to 3% of patients, regardless of drug relationship: constipation 2.9%, insomnia 2.9%, dizziness 2.9%, injection site pain 2.7%, vomiting 2.2%, abdominal pain 2.6%, dyspepsia 2.5%, rash 1.7%, vaginitis 1.6%, injection site inflammation 1.5%, flatulence 1.6%, pruritus 1.5%, pain 1.4%, fatigue 1.3%, chest pain 1.1%, back pain 1.2%.

The following adverse events occurred in clinical trials at a rate of 0.5 to less than 1%, regardless of drug relationship: anorexia, anxiety, arthralgia, coughing, dry mouth, dyspnea, ear disorder, edema, fever, fungal infection, genital pruritus, increased sweating, skin disorder, somnolence.

In clinical trials, the following events of potential medical importance, occurred at a rate of less than 0.5% regardless of drug relationship: abnormal coordination, abnormal dreaming, abnormal hepatic function, abnormal platelets, abnormal renal function, abnormal vision, acute renal failure, aggravated diabetes mellitus, aggressive reaction, anemia, angina pectoris, ARDS, arrhythmia, arthritis, asthma, bradycardia, cardiac arrest, cerebrovascular disorder, circulatory failure,

coma, confusion, convulsions (seizures), coronary thrombosis, delirium, depression, diplopia, embolism-blood clot, emotionally lability, erythema nodosum, G.I. hemorrhage, granulocytopenia, hallucination, heartblock, hepatic coma, hypoglycemia, hypotension, impaired concentration, increased LDH, jaundice, leukocytosis, leukopenia, lymphadenopathy, manic reaction, mental deficiency, muscle weakness, pancreatitis, paralysis, paranoia, postural hypotension, pseudomembranous colitis, rhabdomyolysis, sleep disorders, speech disorder, stupor, syncope, tachycardia, tendinitis, thrombocytopenia, vertigo, weight decrease, WBC abnormal not otherwise specified, withdrawal syndrome.

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.

Crystalluria and cylindruria have been reported with other quinolones.

The following laboratory abnormalities appeared in 2.1 to 2.3% 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

OVERDOSAGE

According to toxicity studies in animals, the most important signs to be expected following acute overdosage of LevoxinTM solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness and convulsive seizures. In the event of relevant overdosage, symptomatic treatment should be implemented. Hemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

PHARMACEUTICAL PARTICULARS

INCOMPATIBILITIES

Levofloxacin infusion IV should not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate).

SHELF LIFE

shelf life after removal of the outer packing is 3 days (under indoor light condition). No protection from light is necessary during infusion.

USE/HANDLING INSTRUCTIONS

Levox™ should be used immediately (with in 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

MIXTURE WITH OTHER SOLUTIONS FOR INFUSIONS

Levox™ solution for infusion is compatible with the following solutions for infusion:

- 0.9% Sodium Chloride solution BP
- 5% Dextrose Injection BP
- 2.5% Dextrose in Ringer solution and combination solutions for Parenteral nutrition

EXPIRY DATE

Do not use later than the date of expiry.

Keep medicines out of reach of children.

PRESENTATION

Levox™ is available as 100 ml infusion plastic bottle containing 5 mg/ml of Levofloxacin in Water for Injections BP.

STORAGE

Store below 25°C. Protect from light, freezing & an excessive heating.

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 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 in-tolerant 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%) [95% CI of -19,-6]. In the second study, 264 patients were enrolled in a prospective, multi-center, noncomparative 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%, 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

ANIMAL PHARMACOLOGY

Levofloxacin and other quinolones have been shown to cause arthropathy in immature animals of most species tested. In immature dogs (4-5 months old), oral doses of 10 mg/ kg/ day for 7 days and intravenous doses of 4 mg/ kg/ days 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.

Manufactured by :
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