SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin Infusion 5 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 100 mL contains

Levofloxacin Hemihydrate USP

Eq. Levofloxacin .....500 mg

Anhydrous Glucose BP .....5% w/v

Water for Injections BP.....q.s

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear yellow or greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Levofloxacin Infusion 5 mg/mL is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Community - acquired pneumonia.
- Complicated skin and soft tissue infections

For the above-mentioned infections levofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections

- Pyelonephritis and complicated urinary tract infections (see section 4.4)
- Chronic bacterial prostatitis
- Inhalation anthrax: postexposure prophylaxis and curative treatment (see section 4.4)

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Levofloxacin Infusion 5 mg/mL is administered by slow intravenous infusion once or twice daily. The dosage depends in the type and severity of the infection and the susceptibility of the presumed causative pathogen. Treatment with levofloxacin after the initial use of the intravenous preparation may be completed with an appropriate oral levofloxacin presentation, in accordance with it's SPC, and as considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology:

The following dose recommendations can be given for levofloxacin:

Dosage in patients with normal renal function (creatinine clearance > 50 ml/min)

Indication	**Daily dose regimen** (according to severity)	**Total duration of Treatment**[1] (according to severity)
Community-acquired pneumonia	500 mg once or twice daily	7-14 days
Pyelonephritis	500 mg once daily	7-10 days
Complicated urinary tract infections	500 mg [1] once daily	7-14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7-14 days
Inhalation anthrax	500 mg once daily	8 weeks

[1]Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation, but is normally 2 to 4 days.

Special populations:

Patients with renal impairment (creatinine clearance ≤ 50 ml/min)

	Dose regimen		
	250 mg/24 h	**500 mg/24 h**	**500 mg/12 h**
Creatinine clearance	first dose: 250 mg	first dose: 500 mg	first dose: 500 mg
50 - 20 mL/min	then: 125 mg/24 h	then: 250 mg/24 h	then : 250 mg/12 h
19-10 mL/min	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/12 h
< 10 mL/min (including haemodialysis and CAPD)[1]	then: 125 mg/48 h	then: 125 mg/24 h	then: 125 mg/24 h

[1]No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

Patients with hepatic impairment

No adjustment of dose is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Older people

No adjustment of dose is required in the elderly, other than that imposed by consideration of renal function (see section 4.4 ' tendinitis and tendon rupture' and 'QT interval prolongation').

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents (see section 4.3).

Method of administration

Levofloxacin solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg levofloxacin (see section 4.4).

For incompatibilities see 6.2

4.3 Contraindications

Levofloxacin Infusion 5 mg/mL must not be used:

- In patients hypersensitive to levofloxacin, to any other quinolones or to any of the excipients listed in section 6.1
- In patients with epilepsy
- In patients with history of tendon disorders related to fluoroquinolone administration
- In children or growing adolescents
- During pregnancy
- In breast-feeding women

4.4 Special warnings and precautions for use

Methicillin-resistant *Staphylococcus aureus* (MRSA) are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed

susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA infections are considered inappropriate).

Resistance to fluoroquinolones of *E. Coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *E.Coli to* fluoroquinolones.

Inhalation Anthrax: Use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Infusion time

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg levofloxacin should be observed. It is known for ofloxacin, that during infusion tachycardia and a 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, (l-isomer of ofloxacin) the infusion must be halted immediately.

Blood Glucose Disturbances

As with other fluoroquinolones, disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported with Levofloxacin Infusion 5 mg/mL, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glyburide) or with insulin. In these patients, careful monitoring of blood glucose is recommended. If a hypoglycemic reaction occurs in a patient being treated with Levofloxacin Infusion 5 mg/mL, Levofloxacin Infusion 5 mg/mL should be discontinued and appropriate therapy should be initiated immediately.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance (see Section 4.2) Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon (see sections 4.3 and 4.8)

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin, (including several weeks after treatment) may be symptomatic of Clostridium difficile-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis (see section 4.8). It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Antiperistaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizuresQuinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, (see section 4.8), treatment with levofloxacin should be discontinued. ***Patients with G-6- phosphate dehydrogenase deficiency***

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose medicinal product should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Levofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported , usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial ultraviolet (UV) rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation, in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and selfendangering behaviour - sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

QT interval prolongation

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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)*
- *uncorrected electrolyte imbalance (e.g hypokalaemia, hypomagnesaemia)*
- *cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)*
- *elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquiolones, including levofloxacin, in these populations.*

(See section 4.2 Elderly, 4.5, 4.8, and 4.9).

Peripheral neuropathy

Peripheral sensory neuropathy and peripheral motor sensory neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset (see

section 4.8). Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of Mycobacterium tuberculosis and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin

Theophylline, fenbufen or similar non-steroidal 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, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

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 effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digioxin, glibenclamide, ranitidine.

Effect of Levofloxacin on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists (see section 4.4).

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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics). (See section 4.4 QT interval prolongation).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

4.6 Fertility, pregnancy and lactation *Pregnancy*

There are limited amount of data on the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3) However in the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism levofloxacin must not be used during pregnancy (see sections 4.3 and 5.3).

Breast Feeding

Levofloxacin is contraindicated in breast-feeding women. There is insufficient evidence on the excretion of Levofloxacin in human milk, however other fluoroquinolones are excreted in human breast milk. In the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, and visual disturbances) 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 (e.g. driving a car or operating machinery).

4.8 Undesirable effects

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies in this table are defined using the following convention:

Very common: (≥1/10)

Common: (≥1/100 to <1/10)

Uncommon: (≥1/1000 to <1/100)

Rare: (≥1/10000 to <1/1000)

Very rare: (< 1/10000)

Not known (Cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Common** (≥1/100 to <1/10)	**Uncommon** (≥1/1,000 to <1/100)	**Rare** (≥1/10,000 to <1/1,000)	**Not known** (cannot be estimated from available data)
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and the lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angiodema Hypersensitivity (see section 4.4)	Anaphylactic[a] shock and Anaphylactoid[a] shock (see section 4.4)

Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)	Hyperglycaemia Hypoglycaemic coma (see section 4.4)
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with eg hallucination, paranoia), Depression Agitation Abnormal dreams Nightmares	Psychotic with selfendangering behaviour including suicidal ideation or suicide attempt (see section 4.4)
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion (see sections 4.3 and 4.4) Paraesthesia	Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision (see section 4.4)	Transient vision loss (see section 4.4)
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia, Which may result in cardiac arrest. Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9)
Vascular disorders	Phlebitis		Hypotension	

Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting	Abdominal pain Dyspepsia		Diarrhoea – haemorrhagic which

	Nausea	Flatulence Constipation		in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including fatal cases with acute liver failure , primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon, Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4))	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions	Infusion site reaction (pain, reddening)	Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

[a]Anaphylactic and anaphalactoid reactions may sometimes occur, even after the first dose

[b]Mucocutaneous reactions may sometimes occur even after the first dose

Other undesirable effects which have been associated with fluoroquinolone administration include: [illegible]

porphyria.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of

levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.
CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials - Fluoroquinolones

ATC Code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (C_{max}) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both Type II topoisomerases, DNA gyrase and topisomeras IV. Other resistance mechanisms, such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L):

EUCAST clinical MIC breakpoints for levofloxacin Version 2.0, 2012-01-01

Pathogen	Susceptible	Resistant
Enterobacteriaceae	≤1 mg/L	>2 mg/L
Pseudomonas spp.	≤1 mg/L	>2 mg/L
Acinetobacter spp.	≤1 mg/L	>2 mg/L
Staphylococcus spp.	≤1 mg/L	>2 mg/L
S. pneumoniae[1]	≤2 mg/L	>2 mg/L
Streptococcus A,B,C,G	≤1 mg/L	>2 mg/L
H. influenzae[2,3]	≤1 mg/L	>1 mg/L
M. catarrhalis[3]	≤1 mg/L	>1 mg/L
Non-species related breakpoints[4]	≤1 mg/L	>2 mg/L

[1] The breakpoints for levofloxacin relate to high dose therapy.

[2] Low-level fluoroquinolone resistance (ciprofloxacin MIC's of 0.12-0.5 mg/L) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with H. influenzae.

[3] Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

[4] Breakpoints apply to an oral dose of 500mg x1 to 500mg x2 and an intravenous dose of 500mg x 1 to 500mg x 2.

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram-positive bacteria

Bacillus anthracis

Staphylococcus aureus methicillin-susceptible

Staphylococcus saprophyticus

Streptococci, groups C and G

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Aerobic Gram-negative bacteria

Eikenella corrodens

Haemophilus influenzae

Haemophilus para-influenzae

Klebsiella oxytoca

Moraxella catarrhalis

Pasteurella multocida
Proteus vulgaris

Providencia rettgeri

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydophila pneumoniae

Chlamydophila psittaci

Chlamydia trachomatis

Legionella pneumophila

Mycoplasma pneumoniae

Mycoplasma hominis

Ureaplasma urealyticum

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive bacteria

Enterococcus faecalis

Staphylococcus aureus methicillin-resistant[#]

Coagulase negative Staphylococcusspp

Aerobic Gram-negative bacteria

Acinetobacter baumannii

Citrobacter freundii

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Morganella morganii

Proteus mirabilis

Providencia stuartii

Pseudomonas aeruginosa Serratia
marcescens

Anaerobic bacteria

Bacteroides fragilis

Inherently Resistant Strains

Aerobic Gram-positive bacteria

Enterococcus faecium

 # Methicillin-resistant S.aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

5.2 Pharmacokinetic properties

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 h. The absolute bioavailability is 99 to 100 %.

Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein.

The mean volume of distribution of levofloxacin is approximately 100l after single and repeated 500mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebro-spinal fluid.

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyllevofloxacin 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 of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{1/2}$: 6 - 8h). Excretion is primarily by the renal route (> 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500mg single dose was 175+/- 29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

Special Populations

Subjects with 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:

Pharmacokinetics in renal insufficiency following single oral 500mg dose

Cl_{cr} [ml/min]	< 20	20 - 40
Cl_R [ml/min]	13	26
$t_{1/2}$ [h]	35	27

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.

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats, and its only effect on foetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung (CHL) cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid

exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity assay.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient

Anhydrous Glucose

Edetate Disodium

Sodium Hydroxide

Hydrochloric Acid Water
for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate). This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Do not store above 30°C. Protect from light. Do not freeze.

Keep out of the sight and reach of children.

6.5 Nature and contents of container 100mL
Solution in LDPE bottles.

6.6 Special precautions for disposal and other handling This product is for single use only.

No protection from light is necessary during infusion.

Any unused product or waste material should be disposed of in accordance with local requirements.