Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5 mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 5 mg levofloxacin as levofloxacin hemihydrate.
Each 50 ml vial of Levofloxacin 5mg/ml Solution for infusion contains 250 mg of levofloxacin as levofloxacin hemihydrate.
Each 100 ml vial of Levofloxacin 5mg/ml Solution for infusion contains 500 mg of levofloxacine as levofloxacin hemihydrate.
Excipients:
Contains 7.7 mmol (177 mg) sodium per 50 ml of solution for infusion.
Contains 15.4 mmol (354 mg) sodium per 100 ml of solution for infusion.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless to yellow to greenish-yellow solution (iso-osmetic, pH about 4.1-5.1).

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults for whom intravenous therapy is considered to be appropriate, Levofloxacin solution for infusion is indicated for the treatment of the following infections (see section 5.1):

- Community-acquired pneumonia
- Complicated urinary tract infections including pyelonephritis
- Chronic bacterial prostatitis
- Skin and soft tissue infections

Before prescribing levofloxacin, consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Levofloxacin solution for infusion is administered by **slow** intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection, and the sensitivity of the presumed causative pathogen. It is usually possible to switch from initial intravenous treatment to the oral route after a few days (Levofloxacin 250 or 500 mg film-coated tablets), according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Duration of treatment
The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Levofloxacin (solution for infusion or tablets) should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

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 solution for infusion** (see section 4.4). It is possible to switch from an initial intravenous application to the oral route at the same dosage after a few days, according to the condition of the patient.
For incompatibilities see section 6.2.
For compatibilities with other infusion solutions see section 6.6.

Posology:
The following dose recommendations can be given for Levofloxacin infusion:

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

Indication	**Daily dose regimen** *(according to severity)*
Community-acquired pneumonia	500 mg once or twice daily
Complicated urinary tract infections including pyelonephritis	250 mg once daily*
Chronic bacterial prostatitis	500 mg once daily
Skin and soft tissue infections	500 mg twice daily

** Consideration should be given to increasing the dose in cases of severe infection and special attention should be paid to available information on resistance to levofloxacin before commencing therapy. Because of the increasing E.coli resistance the dose 500 mg/day should be considered.*

Dosage in patients with impaired renal function
(creatinine clearance ≤50ml/min)

Creatinine clearance	**Dose regimen**		
	250 mg/24h	**500 mg/24h**	**500 mg/12h**
	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).

Dosage in patients with impaired liver function
No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Dosage in elderly
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function - those associated with differences in creatinine clearance *(*see *Dosage in patients with impaired renal function).*

Use in children and adolescents
Levofloxacin is contraindicated in children or growing adolescents (up to age of 18, see section 4.3).

4.3 Contraindications

- Hypersensitivity to levofloxacin or other quinolone derivates or to any of the excipients.
- Patients with epilepsy.
- Patients with history of tendon disorders related to fluoroquinolone administration.
- Children or growing adolescents (up to age of 18).
- Pregnancy.
- Breast-feeding women.

4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia levofloxacin may not be the optimal therapy.
Nosocomial infections due to P. aeruginosa may require combination therapy.
Methicillin-resistant *S. aureus* 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 (see section 5.1).

Infusion time

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg Levofloxacin solution for infusion 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.

Tendonitis and tendon rupture
Tendonitis, which is observed in rare cases during treatment with quinolones, may sometimes lead to tendon rupture, particularly of the Achilles tendon. The risk of tendonitis and tendon rupture is increased in the elderly (over 65 years) and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin. Patients should be warned to consult their physician if they experience symptoms of tendonitis.
If tendonitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile - associated disease
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin infusion, may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Levofloxacin infusion must be stopped immediately and patients should be treated symptomatically without delay, and where necessary with specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures
Levofloxacin 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 pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory medicinal products or with medicinal products which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, 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 levofloxacin therapy should be used with caution.

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin 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.

Hypoglycaemia
As with all quinolones, hypoglycaemia has been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g., glibenclamide) or with insulin. In these diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Prevention of photosensitisation
Although photosensitisation occurs very rarely during treatment with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists
Due to raised values of coagulation parameters (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation parameters should be monitored when these medicinal products 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 self-endangering 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 medicinal products that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- (See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

Peripheral neuropathy
Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Opiates
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.

Hepatobiliary disorders
Cases of hepatic necrosis up to life threatening 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.

This medicinal product contains 354 mg (15.4 mmol) sodium per 100 millilitres of solution. To be taken into consideration by patients on a controlled sodium diet.

Myasthenia gravis Levofloxacine can exacerbate the symptoms of myasthenia gravis which may result in life threatening weakness of respiratory muscles. Adequate counter measures should be taken at any sign of respiratory distress (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Theophylline, fenbufen or similar non-steroidal anti-inflammatory medicinal products
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 medicinal products, 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 medicinal products 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 coadministered with medicinal products that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Cyclosporine
The half-life of cyclosporin is increased by 33% when co-administered with levofloxacin.

Vitamin K antagonists
Increased values for coagulation parameters (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 parameters, therefore, should be monitored in patients treated with vitamin K antagonists.

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
Clinical pharmacology studies were carried out to investigate possible pharmacokinetic interactions between levofloxacin and commonly used medicinal products. The pharmacokinetics of levofloxacin were not affected to any clinically relevant extent on concomitant administration of the following substances:

- Calcium carbonate
- Glibenclamide
- Ranitidine
- Digoxin

4.6 Fertility, pregnancy and lactation

Pregnancy
Reproductive studies in animals did not raise any specific concern. 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, levofloxacin must not be used in pregnant women (see sections 4.3 and 5.3).

Lactation
In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage in the growing organism, levofloxacin must not be used in breast-feeding women (see sections 4.3 and 5.3).

4.7 Effects on ability to drive and use machines

Levofloxacin has minor or moderate influence on the ability to drive and use machines. Undesirable effects (e.g. dizziness, drowsiness, visual disturbances) may impair the patient's ability to
concentrate and react and constitute a risk factor in situations where these abilities are of special importance (see section 4.8).

4.8 Undesirable effects

The following terminologies (according to MedDRA) have been used in order to classify the occurrence of undesirable effects:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data).

Investigations
Common: hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT).
Uncommon: blood bilirubin increased, blood creatinine increased.

Cardiac disorders
Rare: tachycardia.
Not known: ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see section 4.4 and 4.9)

Blood and lymphatic system disorders:
Uncommon: eosinophilia, leucopenia.
Rare: neutropenia, thrombocytopenia.
Very rare: agranulocytosis.
Not known: haemolytic anaemia, pancytopenia.

Nervous system disorders
Uncommon: headache, dizziness/vertigo, drowsiness.
Rare: paresthesia, tremor, confusion, convulsion.
Very rare: hypoaesthesia, disturbances of taste and smell.

Eye disorders:
Very rare: visual disturbances.

Ear and labyrinth disorders:
Uncommon: vertigo.
Very rare: auditory disturbances.
Not known: tinnitus.

Respiratory, thoracic and mediastinal disorders
Rare: bronchospasm, dyspnoea.
Very rare: pneumonitis allergic.

Gastrointestinal disorders
Common: nausea, diarrhoea.
Uncommon: vomiting, abdominal pain, dyspepsia.
Rare: bloody diarrhoea which in very rare cases may be indicative of enterocolitis, membranous including pseudomembranous colitis.

Renal and urinary disorders
Very rare: acute kidney failure (e.g. due to interstitial nephritis).

Skin and subcutaneous tissue disorders
Uncommon: pruritus, rash.
Rare: urticaria.
Very Rare: angioedema, photosensitivity reaction.
Not known: severe bullous eruptions such as Steven's-Johnson syndrome, toxic epidermal necrolysis (Lyell’s syndrome) and erythema exudativum multiforme. Muco-cutaneous reactions may sometimes occur even after the first dose.

Muscoskeletal and connective tissue disorders
Rare: arthralgia, myalgia, tendon disorders including tendonitis (e.g. Achilles tendon (see section 4.4).
Very rare: tendon rupture (e.g. Achilles tendon). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral (see section 4.4). Muscular weakness, which may be of special importance in patients with myasthenia gravis (see section 4.4).
Not known: rhabdomyolysis.

Metabolism and nutrition disorders
Uncommon: anorexia.
Very rare: hypoglycaemia, particularly in diabetic patients (see section 4.4).

Infections and infestations
Uncommon: fungal infection (and proliferation of other resistant microorganisms).

Vascular disorders
Common: phlebitis.
Rare: hypotension.

General disorders and administration site conditions
Common: pain, local reactions at the infusion site.
Uncommon: asthenia.
Very rare: pyrexia.
Not known: pain (including pain in back, chest, and extremities).

Immune system disorders
Very rare: anaphylactoid shock.
Not known: hypersensitivity (see section 4.4).
Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.

Hepatobiliary disorders:
Very rare: hepatitis.
Not known: jaundice and severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (see section 4.4).

Psychiatric disorders
Uncommon: insomnia, nervousness.
Rare: anxiety, depression, psychotic reactions, agitation.
Very rare: hallucinations, psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4).

Others
Other undesirable effects which have been associated with fluoroquinolone administration, include:
- extrapyramidal symptoms and other disorders of muscular coordination,
- hypersensitivity vasculitis,
- attacks of porphyria in patients with porphyria.

4.9 Overdose

According to toxicity studies in animals or clinical studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, convulsive seizures, prolongation of QT interval and gastro-intestinal symptoms in the form of nausea and mucosal erosions.
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

General 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.

Mode 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 (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance
The main mechanism of resistance is due to a gyr-A mutation. In vitro there is a cross-resistance between levofloxacin and other fluoroquinolones. 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 (2009-04-07):

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

[1] *Streptococcus pneumoniae* - wild type *S.pneumoniae* are not considered susceptible to ciprofloxacin or ofloxacin and are therefore categorized as intermediate. For ofloxacin the I/R breakpoint was increased from 1.0 to 4.0 mg/L and for levofloxacin the S/I-breakpoint from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints for levofloxacin relate to high dose therapy.

[2] Strains with MIC values above the S/I 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 sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint (in italics) they should be reported resistant.
Haemophilus/Moraxella - fluoroquinolone low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in *H.influenzae*. There is no evidence that low-level resistance is of clinical importance in respiratory tract infections with *H.influenzae.*

[3] Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for species not mentioned in the table or footnotes.

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. 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: *Staphylococcus aureus** (1) Coagulase negative methicillin-susceptible

Staphylococcus spp including *Staphylococcus saprophyticus*
Streptococci

Aerobic Gram-negative bacteria
Eikenella corrodens
*Haemophilus influenzae **
*Haemophilus para-influenzae **
Klebsiella oxytoca
*Klebsiella pneumoniae **
*Legionella pneumophila**
*Moraxella catarrhalis **
Pasteurella multocida
Proteus vulgaris
Providencia rettgeri

Anaerobic bacteria
Clostridium perfringens
Fusobacterium
Prevotella$
Propionibacterium

Other
Chlamydia trachomatis
Chlamydophila *pneumoniae**
Chlamydophila *psittaci*
Mycoplasma hominis
*Mycoplasma pneumoniae**
Ureaplasma urealyticum

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria
*Enterococcus faecalis**

Aerobic Gram-negative bacteria
*Acinetobacter baumannii **
*Citrobacter freundii **
Enterobacter aerogenes
Enterobacter agglomerans
*Enterobacter cloacae **
*Escherichia coli **
*Morganella morganii **
*Proteus mirabilis**
Providencia stuartii
*Pseudomonas aeruginosa**
*Serratia marcescens**

Anaerobic bacteria
Peptostreptococcus

Inherently resistant organisms
Aerobic Gram-positive bacteria *Enterococcus faecium* **Aerobic Gram-negative bacteria** *Burkholderia cepacia* **Anaerobic bacteria** *Bacteroides* *Clostridium difficile*
∗ Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications. *$ natural intermediate susceptibility* (1) There is a very high rate of co-resistance to fluoroquinolones in cases of methicillin resistant *S. aureus.*

5.2 Pharmacokinetic properties

Distribution
Approximately 30 - 40% of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable accumulation of levofloxacin after doses of 500 mg 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 p.o. were 8.3 microgram/g and 10.8 microgramg/mL, respectively. These were reached approximately one hour after administration.

Penetration into lung tissue
Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 microgram/g and were reached between 4 -6 hours after administration. The concentrations in the lungs consistently exceeded the plasma concentration.

Penetration into blister fluid
Maximum levofloxacin concentrations of about 4.0 and 6.7 microgram/mL in the blister fluid were reached 2-4 hours after administration following 3 days' treatment with 500 mg once or twice daily respectively.

Penetration into cerebrospinal fluid
Levofloxacin has poor penetration into cerebrospinal fluid.

Penetration into prostatic tissue
After administration of oral 500 mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7 microgram/g, 8.2 microgram/g and 2 microgram/g respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

Concentration in urine
The mean urine concentrations 8 - 12 hours after a single oral dose of 150 mg, 300 mg or 500 mg Levofloxacin were 44 mg/L, 91 mg/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 of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 - 8 h). Excretion is primarily by the renal route (> 85 % of the administered dose).
There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Patients 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:

Cl_{cr} [mL/min]	<20	20-40	50-80
Cl_R [mL/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

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 showed small to marginal gender differences in levofloxacin pharmacokinetics. The clinical relevance of these differences has not been established.

5.3 Preclinical safety data

Acute toxicity

The median lethal dose (LD_{50}) values obtained in mice and rats after intravenous administration of levofloxacin were in the range 250 - 400 mg/kg; in dogs the LD_{50} , value was approximately 200 mg/kg with one of two animals which received this dose dying.

Repeated dose toxicity

Studies of one month duration with intravenous administration have been carried out in the rat (20, 60, 180 mg/kg/day) and monkey (10, 25, 63 mg/kg/day) and a three-month study has also been carried out in the rat (10, 30, 90 mg/kg/day).
The "No Observed Adverse Effect Levels " (NOEL) in the rat studies were concluded to be 20 and 30 mg/kg/day in the one month and three-month studies respectively. Crystal deposits in urine were seen in both studies at doses of 20 mg/kg/day an above. High doses (180 mg/kg/day for 1 month or 30 mg/kg/day and above for 3 months) slightly decreased food consumption and body weight gain. Haematological examination showed reduced erythrocytes and increased leucocytes an reticulocytes at the end of the 1 month, but not after 3 months.
The NOEL in the monkey study was concluded to be 63 mg/kg/day with only minor reduction in food and water consumption at this dose.

Reproductive toxicity

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/day o intravenous doses up to 100 mg/kg/day.

Levofloxacin was not teratogenic in rats at oral doses as high as 810 mg/kg/day, or at intravenous doses as high as 160 mg/kg/day. No teratogenicity was observed when rabbits were dosed orally with up to 50 mg/kg/day or intravenously with up to 25 mg/kg/day.
Levofloxacin had no effect on fertility and its only effect on foetuses was delayed maturation as a result of maternal toxicity

Genotoxicity

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung (CHL) cells in vitro at or above 100 µg/ml, in the absence of metabolic activation. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Phototoxicity

Studies in the mouse after both intravenous and oral dosing 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.

Carcinogenic potential

No indication of carcinogenic potential was seen in a two-year study in the rat with dietary administration (0, 10, 30 and 10(mg/kg/day).

Toxicity to joints

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 excipients

Sodium chloride
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
The following active substances or solution for reconstitution/dilution should not be administered simultaneously:
- Heparins or alkaline solutions (e.g. sodium hydrogen carbonate) because of physical incompatibility.

6.3 Shelf life

2 years

In use shelf life:
After removal of the outer packaging (carton) the shelf-life is 3 days (under indoor light conditions).
After first opening :
Chemical and physical in use stability has been demonstrated for 3 hours at 25 °C
From microbiological point of view, the product should used immediately.

It is not necessary to protect the solution from light during infusion.

6.4 Special precautions for storage

Store below 25°C.
Keep the vials in the original package, in order to protect from light.
Do not freeze.
For storage conditions of the product, see section 6.3.

6.5 Nature and contents of container

50 ml clear glass vial (type I), containing 50 ml solution for infusion, closed with chlorobutyl rubber stopper and aluminium cap with a flip off polypropylene seal.
Packsizes: 1, 5 vials.
100 ml clear glass vial (type I), containing 100 ml solution for infusion, closed with chlorobutyl rubber stopper and aluminium cap with a flip off polypropylene seal.
Packsizes: 1, 5 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

This product is for single use only.

Levofloxacin solution for infusion should be used immediately.
The solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear or yellow to greenish-yellow clear solution must be used.

Mixture with other solutions for infusion :

Levofloxacin solution for infusion is compatible with the following solutions for infusion :

Sodium chloride 9 mg/ml (0.9%) solution for infusion
Glucose 50 mg/ml (5 %) injection
Ringer solution, glucose 25 mg/ml (2.5%)
Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes)

See 6.2 for incompatibilities.
Inspect the vial before use. It must only be used if the solution is clear, colourless to yellow to greenish-yellow clear solutio free from particles.

Any unused solution should be discarded immediately after initial use.
Any unused product or waste material should be disposed of in accordance with local requirements.

If levofloxacin is administered via the same infusion line that is also used for other medicinal products, it is important that this infusion line is adequately flushed (e.g. with 0.9% sodium chloride) between administration of levofloxacin and medicinal products for which incompatibility with levofloxacin has been demonstrated or for which compatibility with levofloxacin has not been established.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA711/152/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 2009

10 DATE OF REVISION OF THE TEXT

October 2011