

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5mg/ml Solution for infusion, glass bottles.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

500 mg levofloxacin in 100 ml solution for infusion (as 512 mg of levofloxacin hemihydrate).
Each 1 ml of solution for infusion contains 5 mg levofloxacin (as 5.12 mg levofloxacin hemihydrate).

Excipient(s) with known effect:

1 ml of solution for infusion contains approximately 154 micromol (3.54 mg) sodium
Each 100 ml of solution of infusion contains 15.4mmol (354mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion

Levofloxacin 5 mg/ml Solution for infusion is a clear yellow to greenish-yellow solution with pH ranging from 3.80 to 5.80 and osmolality ranging from 270 to 340 mOsmol/kg

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 when due to levofloxacin-susceptible microorganisms (see sections 4.4 and 5.1):

- Community-acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Chronic bacterial prostatitis.
- Skin and soft tissue infections (caused by Gram-negative bacteria)

Before prescribing Levofloxacin, consideration should be given to official guidance on the appropriate use of fluoroquinolones

4.2 Posology and method of administration

Posology

The following dose recommendations can be given for Levofloxacin 5 mg/ml Solution for infusion:

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

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

Special populations

Renal impairment (creatinine clearance ≤ 50ml/min)

	Dose regimen		
	250 mg/24 h	500 mg/24 h	500 mg/12 h
Creatinine clearance	<i>first dose:</i> 250 mg	<i>first dose:</i> 500 mg	<i>first dose:</i> 500 mg
50 - 20 ml/min	<i>then:</i> 125 mg/24 h	<i>then:</i> 250 mg/24 h	<i>then :</i> 250 mg/12 h
19 - 10 ml/min	<i>then:</i> 125 mg/48 h	<i>then:</i> 125 mg/24 h	<i>then:</i> 125 mg/12 h
< 10 ml/mi (including haemodialysis and CAPD) ¹	<i>then:</i> 125 mg/48 h	<i>then:</i> 125 mg/24 h	<i>then:</i> 125 mg/24 h

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

Hepatic impairment

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.

Elderly population

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function (see section 4.4 QT interval prolongation).

Paediatric population

Levofloxacin 5 mg/ml Solution for infusion is contraindicated in children and growing adolescents under 18 years of age (see section 4.3).

Duration of treatment

The duration of treatment varies according to the course of the disease. As with antibiotic therapy in general, administration of Levofloxacin Solution for infusion 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 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, according to the condition of the patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

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 instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, any other quinolone and to any of the excipients listed in section 6.1,
- Patients with epilepsy,
- Patients with history of tendon disorders related to fluoroquinolone administration,
- Children or growing adolescents (**up to age of 18**),
- During pregnancy,
- Breast-feeding women.

4.4 Special warnings and precautions for use

In the most severe cases of pneumococcal pneumonia Levofloxacin 5mg/ml Solution for infusion may not be the optimal therapy.

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

Methicillin-resistant *Staphylococcus aureus* (MRSA)

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.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. 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.

***Clostridium difficile*-associated disease**

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

Patients predisposed to seizures

Levofloxacin 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 damage, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs or with drugs 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, and so levofloxacin should be used with caution.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of Levofloxacin solution for infusion 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.

Hypoglycemia

As with all quinolones, hypoglycemia 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 photosensitization

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 (e.g. sunray lamp, solarium), 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 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.

Cardiac disorders

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

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- 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 fluoroquinolones, including levofloxacin, in these populations.

(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.

Myasthenia gravis

Levofloxacin 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).

This medicinal product contains 15.4 mmol (354 mg) sodium per 100 ml of solution. To be taken into consideration by patients on a controlled sodium diet. Refer to section 2 for sodium contents in each pack size.

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 coadministered with drugs that affect 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, digoxin, 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).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data with respect to 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). In juvenile and pre natal animals exposed to quinolones, effects on immature cartilage have been observed; thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / fetus (see section 5.3). The product is therefore contraindicated during pregnancy.

Breast-feeding

There is insufficient information with respect to the excretion of levofloxacin in human and/or animal milk. In the absence of these data and given the potential risk of articular damage, levofloxacin is contraindicated during breast-feeding.

Fertility

Animal studies indicate that levofloxacin has no effect on fertility

4.7 Effects on ability to drive and use machines

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, 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 5000 patients and on extensive post marketing experience.

The adverse reactions are described according to the MedDRA system organ class in the table below.

Frequencies are defined using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $\leq 1/100$), rare ($\geq 1/10000$, $\leq 1/1000$), very rare ($\leq 1/10000$), not known (cannot be estimated from the available data).

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

Infections and infestations

Uncommon: Fungal infection (and proliferation of other resistant microorganisms)

Blood and lymphatic system disorders

Uncommon: Leukopenia, eosinophilia

Rare: Thrombocytopenia, neutropenia

Very rare: Agranulocytosis

Not Known: Pancytopenia, haemolytic anaemia

Immune system disorders

Very rare: Anaphylactic shock (see section 4.4)

Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

Not known: Hypersensitivity (see section 4.4)

Metabolism and nutrition disorders

Uncommon: Anorexia

Very rare: Hypoglycemia, particularly in diabetic patients (see section 4.4)

Psychiatric disorders

Uncommon: Insomnia, nervousness

Rare: Psychotic disorder, depression, confusional state, agitation, anxiety

Very rare: Psychotic reactions with self-endangering behaviour including suicidal ideation or acts (see section 4.4), hallucination

Nervous system disorders

Uncommon: Dizziness, headache, somnolence

Rare: Convulsion, tremor, paraesthesia

Very rare: sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia

Eye disorders

Very rare: Visual disturbance

Ear and Labyrinth disorders

Uncommon: Vertigo

Very rare: Hearing impaired

Not known: Tinnitus

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)

Vascular disorders

Common: Phlebitis

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Rare: Bronchospasm, dyspnoea

Very rare: Pneumonitis allergic

Gastrointestinal disorders

Common: Diarrhoea, nausea

Uncommon: Vomiting, abdominal pain, dyspepsia, flatulence, constipation

Rare: Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis

Hepatobiliary disorders

Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)

Uncommon: Blood bilirubin increased

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).

Skin and subcutaneous tissue disorders

Uncommon: Rash, pruritus

Rare: Urticaria

Very rare: Angioneurotic oedema, photosensitivity reaction

Not Known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis

Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and Connective tissue disorders

Rare: Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia

Very rare: Tendon rupture (see section 4.4). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis

Not Known: Rhabdomyolysis

Renal and urinary disorders

Uncommon: Blood creatinine increased

Very rare: Renal failure acute (e.g. due to nephritis interstitial)

General disorders and administration site conditions

Common: Infusion site reaction

Uncommon: Asthenia

Very rare: Pyrexia

Not known: Pain (including pain in back, chest, and extremities)

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 pharmacology 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, and convulsive seizures, increases in QT interval.

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: Antibacterials for systemic use - 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
Enterobacteriaceae	≤1 mg/L	>2 mg/L
<i>Pseudomonas spp.</i>		
<i>Acinetobacter spp.</i>		
<i>Staphylococcus spp.</i>		
<i>Streptococcus A,B,C,G</i>		
Non-species related breakpoints ³		
<i>S.pneumoniae</i> ¹	≤2 mg/L	>2 mg/L
<i>H.influenzae M.catarrhalis</i> ²	≤1 mg/L	>1 mg/L
<div><p>¹<i>Streptococcus pneumoniae</i> - wild type <i>S.pneumoniae</i> 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.</p><p>²Strains 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.</p><p><i>Haemophilus/Moraxella</i> - fluoroquinolone</p><p>low-level resistance (ciprofloxacin MIC:s of 0.125 - 0.5 mg/L) may occur in <i>H.influenzae</i>. There is no evidence that low-level resistance is of clinical</p></div>		

importance in respiratory tract infections with *H.influenzae*.

³Non-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

<u>Commonly susceptible species</u>
<u>Aerobic Gram-positive bacteria</u> <u>Staphylococcus aureus* methicillin-susceptible</u> <u>Coagulase negative meticillin-susceptible</u> <u>Staphylococcus, including staphylococcus saprophyticus</u> <u>Streptococci</u>
<u>Aerobic Gram- negative bacteria</u> <u>Eikenella corrodens</u> <u>Haemophilus influenzae *</u> <u>Haemophilus para-influenzae *</u> <u>Klebsiella oxytoca</u> <u>Klebsiella pneumoniae *</u> <u>Legionella pneumophila*</u> <u>Moraxella catarrhalis *</u> <u>Pasteurella multocida</u> <u>Proteus vulgaris</u> <u>Providencia rettgeri</u>
<u>Anaerobic bacteria</u> <u>Clostridium perfringens</u> <u>Fusobacterium</u> <u>Prevotella(\$).</u> <u>Propionibacterium</u>
<u>Other</u> <u>Chlamydophila pneumoniae *</u> <u>Chlamydophila psittaci</u> <u>Chlamydia trachomatis</u> <u>Mycoplasma pneumoniae *</u> <u>Mycoplasma hominis</u> <u>Ureaplasma urealyticum</u>
<u>Species for which acquired resistance may be a problem</u>
<u>Aerobic Gram-positive bacteria</u> <u>Enterococcus faecalis*</u> <u>Staphylococcus aureus methicillin-resistant</u> <u>Staphylococcus coagulase negative methicillin-resistant</u>
<u>Aerobic Gram- negative bacteria</u> <u>Acinetobacter baumannii *</u> <u>Citrobacter freundii *</u> <u>Enterobacter aerogenes</u> <u>Enterobacter agglomerans</u>

<u>Enterobacter cloacae *</u> <u>Escherichia coli *</u> <u>Morganella morganii *</u> <u>Proteus mirabilis *</u> <u>Providencia stuartii</u> <u>Pseudomonas aeruginosa*</u> <u>Serratia marcescens *</u>
<u>Anaerobic bacteria</u> <u>Peptostreptococcus</u>
<u>Naturally resistant species</u>
<u>Aerobic Gram-positive bacteria</u> <u>Enterococcus faecium</u>
<u>Aerobic Gram-negative bacteria</u> <u>Burkholderia cepacia</u>
<u>Anaerobic bacteria</u> <u>Bacteroides</u> <u>Clostridium difficile</u>
<u>*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.</u>
<u>\$ natural intermediate susceptibility</u>

Other information

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

5.2 Pharmacokinetic properties

Absorption

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

Food has little effect on the absorption of levofloxacin.

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 µg/g and 10.8 µg/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 µg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.

Penetration into Blister Fluid

Maximum levofloxacin concentrations of about 4.0 and 6.7 µg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily respectively.

Penetration into Cerebro-Spinal Fluid

Levofloxacin has poor penetration into cerebro-spinal 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 µg/g, 8.2 µg/g and 2.0 µg/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.

Biotransformation

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.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

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:

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 pharmacokinetics 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

Acute toxicity

The median lethal dose (LD50) values obtained in mice and rats after intravenous administration of levofloxacin were in the range 250-400 mg/kg; in dogs the LD50 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 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 and 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 and reticulocytes at the end of the 1 month, but not the 3 months study.

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 or 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 fetuses 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.

Phototoxic potential

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 100 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
Sodium hydroxide (for pH adjustment)
Hydrochloric acid, (for pH adjustment)
Water for injection

6.2 Incompatibilities

Levofloxacin 5 mg/ml Solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Shelf life as packaged for sale: 2 years

Shelf life after removal of the outer carton – to be used immediately

Shelf life after perforation of the rubber stopper: (see section 6.6).

From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Do not freeze.

Keep bottle in the outer carton in order to protect from light (see section 6.3). Inspect visually prior to use. Only clear solutions without particles should be used.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml type I glass bottle with aluminium cap, bromobutyl rubber stopper and flip off seal. Each bottle contains 100 ml of solution for infusion. Packs of 1, 5, and 10 x 100 ml bottles are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levofloxacin Solution for infusion should be used immediately (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination.

No protection from light is necessary during infusion.

For single use only. Discard any unused solution.

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

Mixture with other solutions for infusion:

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

0.9 % sodium chloride solution USP.

5 % dextrose injection USP.

2.5 % dextrose in Ringer solution.

Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

See section 6.2 for incompatibilities.

7 MARKETING AUTHORISATION HOLDER

Amneal Pharma Europe Limited
70 Sir John Rogerson's Quay
Dublin 2
Ireland

8 MARKETING AUTHORISATION NUMBER

PA 1897/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 28th September 2012

10 DATE OF REVISION OF THE TEXT

June 2013