# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5 mg/ml Solution for Infusion

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

250 mg levofloxacin (as hemihydrate) in 50 ml solution.
500 mg levofloxacin (as hemihydrate) in 100 ml solution.
1 ml of solution for infusion contains 5 mg levofloxacin.

Each 50 ml bag contains approximately 7,7 mmol (177 mg) sodium.
Each 100 ml bag contains approximately 15,4 mmol (354 mg) sodium.
1 ml of solution for infusion contains approximately 154 micromol (3,54 mg) sodium.

For a 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 a greenish-yellow solution with pH ranging from 3.8 to 5.8 and osmolality ranging from 285 to 310 mOsm/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:

• Community-acquired pneumonia (when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection).

• Complicated urinary tract infections including pyelonephritis.

• Chronic bacterial prostatitis.

• Skin and soft tissue infections.

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

### 4.2 Posology and method of administration

*Intravenous use*
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, 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 treatment varies according to the course of the disease. As with antibiotic therapy in general, administration of levofloxacin 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 special precautions for disposal and other handling see section 6.6.

***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)* |
|---|---|
| Community-acquired pneumonia | 500 mg once or twice daily |
| Complicated urinary tract infections including pyelonephritis | 250 mg[1] once daily |
| Chronic bacterial prostatitis | 500 mg once daily |
| Skin and soft tissue infections | 500 mg twice daily |

[1]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.

***Dosage in patients with impaired renal function*** (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).

***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 the elderly***
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).

***Dosage in children and adolescents***
Levofloxacin is contraindicated in children and growing adolescents under 18 years of age (see section 4.3).

## 4.3 Contraindications

- Hypersensitivity to the active substance, any other quinolone or to any of the excipients,
- Patients with epilepsy,
- Patients with history of tendon disorders related to fluoroquinolone administration,
- Children or growing adolescents under 18 years of age,

- During 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.

***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.

***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).

***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 treatment must be stopped immediately and patients should be treated with supportive measures and 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 lesions, 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 glucose−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 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 photosensitisation***
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (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.

***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).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See sections 4.2, 4.5, 4.8, 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.

Levofloxacin contains sodium, approximately 154 micromol/ml (3,54 mg/ml). To be taken into consideration by patients on a controlled sodium diet and in cases where fluid restriction is required.

## 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) (see section 4.4 QT interval prolongation).

## 4.6 Fertility, pregnancy and lactation

*Pregnancy*

Reproductive studies in animals did not raise specific concern. However in the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, 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 of the growing organism, Levofloxacin solution for infusion 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

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 for levofloxacin.

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

Frequencies in the list are defined using the following convention:
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)

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: Electrocardiogram QT prolonged (see section 4.4 QT interval prolongation and section 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 overdose 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: 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**
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.* | ≤1 mg/L | >2 mg/L |
| *Acinetobacter spp.* | ≤1 mg/L | >2 mg/L |
| *Staphylococcus spp.* | ≤1 mg/L | >2 mg/L |
| *Streptococcus pneumoniae* [1] | ≤2 mg/L | >2 mg/L |
| *Streptococcus A,B,C,G* | ≤1 mg/L | >2 mg/L |
| *H.influenzae*<br>*M.catarrhalis* [2] | ≤1 mg/L | >1 mg/L |
| Non-species related breakpoints[3] | ≤1 mg/L | >2 mg/L |

[1] the S/I-breakpoint was increased from 1.0 to 2.0 to avoid dividing the wild type MIC distribution. The breakpoints 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.

[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 that have not been given a species-specific breakpoint and are not for use with species where susceptibility testing is not recommended or for which there is insufficient evidence that the species in question is a good target (*Enterococcus*, *Neisseria*, Gram negative anaerobes)

The CLSI (Clinical And Laboratory Standards Institute, formerly NCCLS) 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 (µg/mL) or disc diffusion testing (zone diameter [mm] using a 5 µg levofloxacin disc).

*CLSI recommended MIC and disc diffusion breakpoints for levofloxacin (M100-S17, 2007):*

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacteriaceae | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| Non Enterobacteriaceae. | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| *Acinetobacter spp.* | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| *Stenotrophomonas maltophilia* | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| *Staphylococcus spp.* | ≤1 µg/mL<br>≥19 mm | ≥4 µg/mL<br>≤15 mm |
| *Enterococcus spp.* | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| *H.influenzae*<br>*M.catarrhalis* [1] | ≤2 µg/mL<br>≥17 mm | |
| *Streptococcus pneumoniae* | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |
| *beta-hemolytic Streptococcus* | ≤2 µg/mL<br>≥17 mm | ≥8 µg/mL<br>≤13 mm |

[1] The absence or rare occurrence of resistant strains precludes defining any results categories other than “susceptible”. For strains yielding results suggestive of a “nonsuceptible” category, organism identification and antimicrobial susceptibility test results should be confirmed by a reference laboratory using CLSI reference dilution method.

**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** methicillin-susceptible
*Staphylococcus saprophyticus*
Streptococci, group C and G

*Streptococcus agalactiae*
*Streptococcus pneumoniae* *
*Streptococcus pyogenes* *

Aerobic Gram-negative bacteria
*Burkholderia cepacia*$
*Eikenella corrodens*
*Haemophilus influenzae* *
*Haemophilus para-influenzae* *
*Klebsiella oxytoca*
*Klebsiella pneumoniae* *
*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 *Staphylococcus spp*

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

Anaerobic bacteria
*Bacteroides fragilis*
*Bacteroides ovatus*$
*Bacteroides thetaiotamicron*$
*Bacteroides vulgatus*$
*Clostridium difficile*$

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
$ natural intermediate susceptibility

**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 1 h. 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 po 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 po 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.

**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 ($t_{½}$: 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 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

**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 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 injections

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Levofloxacin 5mg/ml solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).

## 6.3 Shelf life

*Shelf life as packaged for sale:* 2 years
*Shelf life after removal of the outer packaging:* 7 days

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

Keep the bag in the original packaging in order to protect from light. Inspect visually prior to use. Only clear solutions without particles should be used.

## 6.5 Nature and contents of container

The bags are made of M312A material, a 5-layer, polyolefine based co-extruded film, PVC and plasticizer free. The tubing port is made of M916A material, a multi-layer co-extruded connector tubing, PVC and plasticizer free. The twist off port (Spike Port) is composed of MP312 material, PVC and plasticizer free.

The bags are over wrapped with a three layers formable film constituted by Polyester/Polyester metallised/Polypropylene.

Each bag contains 50 ml solution and 250 mg levofloxacin or 100 ml of solution and 500 mg levofloxacin.
Packs of 1, 5, 10, 15 and 20 bags.

Not all pack sizes may be marketed.

## 6.6 Special precautions for disposal

Preparation for administration:
1. Inspect before use. It must only be used if the solution is a clear, yellow to greenish- yellow solution, free from particles.
2. Hold with the connection ports uppermost.
3. Twist off the protection cap from the connection port.
4. Insert the piercing pin of the i.v. set into the connection port with a twisting motion.
5. Suspend from a hanger.

No protection from light is necessary during infusion.

For single use only. Discard any unused solution.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Any unused solution and the bags should be adequately disposed of, in accordance with local requirements.

## 7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
Reykjavikurvegi 76-78,
220 Hafnarfjordur,
Iceland

## 8 MARKETING AUTHORISATION NUMBER

PA1380/071/001

## 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 10th June 2011

## 10 DATE OF REVISION OF THE TEXT

October 2011