Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin Teva 500 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of levofloxacin corresponding to 512.46 mg of levofloxacin hemihydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Peach, film-coated capsule shaped tablet, debossed with "LX" on the left side and "500" on the right side of the score on one side, scored and smooth on the opposite side.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults with infection of mild or moderate severity Levofloxacin Tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible micro-organisms:

– Acute sinusitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

– Acute exacerbation of chronic bronchitis (adequately diagnosed according to national and/or local guidelines on the treatment of respiratory tract infections, and when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of this infection or when these have failed to resolve the infection),

– 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

Levofloxacin Tablets are administered once or twice daily.
The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

Treatment time
The duration of therapy varies according to the course of the disease (see table below).
As with antibiotic therapy in general, administration of Levofloxacin 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 tablets should be swallowed whole and with sufficient amount of liquid. The tablets may be taken during meals or between meals.

Levofloxacin Tablets should be taken at least two hours before iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

Posology

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

Indication	Daily dose regimen *(depending on severity)*	Duration of the treatment
Acute sinusitis	500 mg once daily	10-14 days
Acute exacerbation of chronic bronchitis	250-500 mg once daily	7-10 days
Community-acquired pneumonia	500 mg once or twice daily	7-14 days
Complicated urinary tract infections including pyelonephritis	250 mg once daily	7 – 10 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Skin and soft tissue infections	250 mg once daily or 500 mg once or twice daily	7 – 14 days

Special populations

Impaired renal function
In patients with creatinine clearance ≤ 50 ml/min dosage should be modified according to the following scheme:

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/24h	then: 250 mg/24h	then: 250 mg/12h
19 - 10 ml/min	then: 125 mg/48h	then: 125 mg/24h	then: 125 mg/12h
< 10 ml/min (including haemodialysis and CAPD) [1]	then: 125 mg/48h	then: 125 mg/24h	then: 125 mg/24h

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

Impaired hepatic 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.

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).

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

4.3 Contraindications

Levofloxacin Tablets must not be used:
- In patients hypersensitive to levofloxacin, other quinolones, or any of the excipients
- In patients with epilepsy
- In patients with history of tendon disorders related to fluoroquinolone administration
- In children or growing adolescents
- During pregnancy
- In breast-feeding women.

4.4 Special warnings and precautions for use

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 *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.

Tendinitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in 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 (see section 4.3 and 4.8).

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

Patients predisposed to seizures
Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with drugs that 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.

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

Prevention of photosensitization
Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp or solarium), in order to prevent photosensitization.

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, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See section 4.2 *Elderl*y, section 4.5, section 4.8, section 4.9).

Peripheral neuropathy
Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset (see section 4.8). Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

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 methods.

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.

Exacerbation of myasthenia gravis
Levofloxacin should be used with caution in patients with a history of myasthenia gravis (see section 4.8).

Superinfection
As with other antibiotics, the use of levofloxacin, especially if prolonged, may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin
Iron salts, magnesium- or aluminium-containing antacids
Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids are administered concomitantly with levofoxacin tablets. It is recommended that preparations containing divalent or trivalent cations such as iron salts, or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after Levofloxacin Tablet administration (see section 4.2). No interaction has been found with calcium carbonate.

Sucralfate
The bioavailability of Levofloxacin Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration (see section 4.2).

Theophylline, fenbufen or similar non-steroidol 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).

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

Other forms of interactions
Meals
There is no clinically relevant interaction with food. Levofloxacin tablets may therefore be administered regardless of food intake.

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 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

Certain 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 5,000 patients and on extensive post-marketing experience.

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

Frequencies are defined using the following convention:
Very common (≥1/10),
Common (≥1/100, <1/10),
Uncommon (≥1/1,000, <1/100),
Rare (≥1/10,000, <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.

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 section 4.9)
Blood and lymphatic system disorders	
Uncommon	Leukopenia, eosinophilia
Rare	Thrombocytopenia, neutropenia
Not known	Pancytopenia, agranulocytosis, haemolytic anaemia
Nervous system disorders	
Common	Headache, dizziness
Uncommon	Somnolence, tremor, dysgeusia
Rare	Convulsions (see section 4.3 and 4.4), paraesthesia
Not known	Peripheral sensory neuropathy (see section 4.4), peripheral sensory motor neuropathy (see section 4.4), parosmia including anosmia, dyskinesia, extrapyramidal disorder, ageusia, syncope
Eye disorders	
Rare	Visual disturbances such as blurred vision
Not known	Transient vision loss
Ear and labyrinth disorders	
Uncommon	Vertigo
Rare	Tinnitus
Not known	Hearing loss, hearing impaired
Respiratory, thoracic and mediastinal disorders	
Uncommon	Dyspnoea
Not known	Bronchospasm, pneumonitis allergic
Gastrointestinal disorders	
Common	Diarrhoea, vomiting, nausea
Uncommon	Abdominal pain, dyspepsia, flatulence, constipation
Not known	Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), pancreatitis
Renal and urinary disorders	
Uncommon	Blood creatinine increased
Rare	Renal failure acute (e.g. due to nephritis interstitial)
Skin and subcutaneous tissue disorders	
Uncommon	Rash, pruritus, urticaria, hyperhidrosis
Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction (see section 4.4), leukocytoclastic vasculitis, stomatitis. Mucocutaneous reactions may sometimes occur even after the first dose.
Musculoskeletal and connective tissue disorders	
Uncommon	Arthralgia, myalgia
Rare	Tendon disorder (see section 4.3 and 4.4) including tendinitis (e.g. Achilles tendon), muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)
Not known	Rhabdomyolysis, tendon rupture (e.g. Achilles tendon) (see section 4.4), muscle rupture, arthritis.
Metabolism and nutrition disorders	
Uncommon	Anorexia
Rare	Hypoglycaemia, particularly in diabetic patients (see section 4.4)
Not known	Hyperglycaemia (see section 4.4)

Infections and infestations	
Uncommon	Fungal infection, pathogen resistance
Vascular disorders	
Rare	Hypotension
General disorders and administration site conditions	
Uncommon	Asthenia
Rare	Pyrexia
Not known	Pain (including pain in back, chest, and extremities)
Immune system disorders	
Rare	Angioedema, hypersensitivity (see section 4.4).
Not known	Anaphylactic shock, anaphylactoid shock (see section 4.4). Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose.
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), hepatitis.
Psychiatric disorders	
Common	Insomnia
Uncommon	Anxiety, confusional state, nervousness
Rare	Psychotic reactions (with e.g. hallucination, paranoia), depression, agitation, abnormal dreams, nightmares
Not known	Psychotic disorders with self-endangering behaviour including suicidal ideation or acts (see section 4.4).

Other undesirable effects, which have been associated with fluoroquinolone administration, include: 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 are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

In the event of overdose symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. 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:	Antiifectives for systemic use – Antibacterials for systemic use – Quinolone antibasterials – 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 (2006-06-20):

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
S. pneumoniae [1]	≤2 mg/L	>2 mg/L
Streptococcus A,B,C,G	≤1 mg/L	>2 mg/L
H. influenzae *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
Enterobacteriacae	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
Non Enterobacteriacae	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
Acinetobacter spp.	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
Stenotrophomonas maltophilia	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
Staphylococcus spp.	≤1 µg/mL ≥19 mm	≥4 µg/mL ≤15 mm
Enterococcus spp.	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
H.influenzae *M.catarrhalis* [1]	≤2 µg/mL ≥17 mm	
Streptococcus pneumoniae	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
Beta-haemolytic Streptococcus	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤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 'non-suceptible' 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 MICROORGANISMS

Aerobic Gram-positive bacteria

*Staphylococcus aureus** methicillin-susceptible
Staphylococcus saprophyticus
Streptococci, groups 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
Staphylococcus haemolyticus methicillin-resistant

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
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
+ More than 50% of resistance

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 hour. 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 three days treatment 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 main metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination
Following oral and intravenous administration, levofloxacin is eliminated relatively slowly from the plasma ($t_{½}$: 6 - 8 hours). 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, showing that the oral and intravenous routes are interchangeable.

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

Patients with renal insufficiency
The pharmacokinetics of levofloxacin is 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
$t_{½}$ [h]	35	27	9

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

Gender differences
Separate analyses 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 LD_{50} values obtained in mice and rats after oral administration of levofloxacin were in the range 1500-2000 mg/kg. Administration of 500 mg/kg orally to monkeys induced little effect apart from vomiting.

Repeated dose toxicity
Studies of one and six months duration by gavage have been carried out in the rat and monkey. Doses were 50, 200, 800 mg/kg/day and 20, 80, 320 mg/kg/day for 1 and 6 months in the rat and 10, 30, 100 mg/kg/day and 10, 25, 62.5 mg/kg/day for 1 and 6 months in the monkey.

Signs of reaction to treatment were minor in the rat with slight effects principally at 200 mg/kg/day and above in reducing food consumption and slightly altering haematological and biochemical parameters.

The 'No Observed Adverse Effect Levels' (NOELs) in these studies were concluded to be 200 and 20 mg/kg/day after 1 and 6 months respectively.
Toxicity after oral dosing in the monkey was minimal with reduced body weight at 100 mg/kg/day together with salivation, diarrhoea and decreased urinary pH in some animals at this dose. No toxicity was seen in the 6-month study. The NOELs were concluded to be 30 and 62.5 mg/kg/day after 1 and 6 months respectively.

The NOELs in the six-month studies were concluded to be 20 and 62.5 mg/kg/day in the rat and monkey respectively.

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 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 cells (CHL) *in vitro* at concentrations 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 oral and intravenous 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 of 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

Tablet core:
Silica, colloidal, anhydrous
Hydroxypropylcellulose
Sodium strach glycolate (type A)
Talc
Croscarmellose sodium
Magnesium stearate

Tablet film-coating:
Hypromellose
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80
Iron oxide, black (E172)
Iron oxide, yellow (E172)
Iron oxide, red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PVdC/aluminium blisters.
Pack sizes: 1, 2, 5, 7, 10, 14, 30, 50 film-coated tablets.
Hospital packs: 50 (5x10) and 200 (20x10) and 500 (50x10) film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

A score line allows adaptation of the dose in patients with impaired renal function.
No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Teva Pharma B.V.
Computerweg 10
3542 DR Utrecht
The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA749/81/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th November 2008
Date of last renewal: 3rd January 2011

10 DATE OF REVISION OF THE TEXT

June 2013