

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin Actavis 250 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Levofloxacin Actavis contains 250 mg of levofloxacin equivalent to 256.23 mg of levofloxacin hemihydrate.

Each 250 mg film-coated tablet contains 3.84 mg of lactose monohydrate.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink biconvex tablets, scored on one side and marked with "L" on the other side. Approximately 13 mm long and 6 mm wide.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

In adults with infections of mild or moderate severity, Levofloxacin Actavis tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute bacterial 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 bacterial exacerbations 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).
- Uncomplicated urinary tract infections.
- 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 and special attention should be paid to available information on resistance to levofloxacin before commencing therapy.

4.2 Posology and method of administration

Levofloxacin Actavis 250 mg 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.

Duration of treatment

The duration of therapy varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin Actavis 250 mg tablets should be continued for a minimum of 48 to 72 hours after the patient has become afebrile (having no fever) or evidence of bacterial eradication has been obtained.

Method of administration

Levofloxacin Actavis 250 mg tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals. Levofloxacin Actavis 250 mg tablets should be taken at least two hours before or after iron salts, antacids and sucralfate administration since reduction of absorption can occur (see section 4.5).

The following dose recommendations can be given for Levofloxacin Actavis 250 mg:

Dosage in patients with normal renal function

(creatinine clearance >50 ml/min)

Indication	Daily dose regimen (according to severity of the infection)	Duration of treatment
Acute sinusitis	500 mg once daily	10 - 14 days
Acute exacerbations of chronic bronchitis	250 to 500 mg once daily	7 - 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Uncomplicated urinary tract infections	250 mg once daily	3 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

Dosage in patients with impaired renal function

(creatinine clearance ≤50ml/min)

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

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

Patients with impaired liver function

Patients with impaired liver function have not been examined in clinical studies. However, no adjustment of dosage is expected to be necessary, since levofloxacin is not metabolised to any great extent by the liver and is mainly excreted by the kidneys.

Elderly patients

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).

Children and adolescents

Levofloxacin Actavis 250 mg is contraindicated in children and growing adolescents (see section 4.3).

4.3 Contraindications

- Hypersensitivity to levofloxacin or other quinolones or any of the excipients.
- Epilepsy.
- History of tendon disorders related to fluoroquinolone administration.
- Children and growing adolescents.
- Pregnancy.
- Breast-feeding women.

4.4 Special warnings and precautions for use

Levofloxacin is not always the optimal therapy in pneumococcal pneumonia, particularly in more severe cases.

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

Methicillin resistant *Staphylococcus aureus* (MRSA)

Levofloxacin is not effective against infections caused by MRSA (see section 5.1). In infections suspicious for MRSA levofloxacin should be combined with an agent approved to treat MRSA infections.

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 immediately if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be stopped 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, treatment with levofloxacin 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.

Hypoglycaemia

As with all quinolones, hypoglycaemia has 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 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 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, neuroleptics, macrolides).
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See section 4.2 *Elderly patients*, 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 a 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 Actavis contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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. 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 Actavis 250 mg tablet administration (see section 4.2). No interaction has been found with calcium carbonate.

Sucralfate

The bioavailability of levofloxacin 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 Actavis 250 mg tablet administration.

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 were carried out to investigate possible pharmacokinetic interactions between levofloxacin and commonly prescribed drugs medicines. 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)

Contraceptive pill

Some antibiotics can in rare cases reduce the efficacy of contraceptive pills by interfering with bacterial hydrolysis of the steroid conjugate in the intestine and thereby the re-absorption of the unconjugated steroid. The plasma levels of the active steroid would by this means be reduced.

Other forms of interactions

Meals

There is no clinically relevant interaction with food. Levofloxacin Actavis 250 mg 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 during breast-feeding (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.

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

Frequencies are defined using the following convention:

Very common ($\geq 1/10$)

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1,000$ to $< 1/100$)

Rare ($\geq 1/10,000$ 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: 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

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.

Hepato-biliary disorders

Common: hepatic enzymes increased (e.g. ALT / AST).

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 (Lyell's syndrome), severe bullous eruptions such as Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis.

Mucocutaneous reactions may sometimes occur even after the first dose.

Musculoskeletal and connective tissue disorders

Rare: tendon disorders (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 (see section 4.4). 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

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 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.

In the event of significant 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: quinolone antibacterials, fluoroquinolones, ATC code: J01MA12

Levofloxacin is a synthetic broad-spectrum 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
Enterobacteriaceae	≤1 mg/L	>2 mg/L
<i>Pseudomonas</i> spp.	≤1 mg/L	>2 mg/L
<i>Acinetobacter</i> spp.	≤1 mg/L	>2 mg/L
<i>Staphylococcus</i> spp.	≤1 mg/L	>2 mg/L

<i>S. pneumoniae</i> ¹	≤2 mg/L	>2 mg/L
<i>Streptococcus</i> A,B,C,G	≤1 mg/L	>2 mg/L
<i>H. influenzae</i> <i>M. catarrhalis</i> 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 ≥17 mm	≥8 µg/mL ≤13 mm
Non Enterobacteriaceae	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
<i>Acinetobacter spp.</i>	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
<i>Stenotrophomonas maltophilia</i>	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
<i>Staphylococcus spp.</i>	≤1 µg/mL ≥19 mm	≥4 µg/mL ≤15 mm
<i>Enterococcus spp.</i>	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
<i>H.influenzae</i> <i>M.catarrhalis</i> ¹	≤2 µg/mL ≥17 mm	
<i>Streptococcus pneumoniae</i>	≤2 µg/mL ≥17 mm	≥8 µg/mL ≤13 mm
<i>Beta-haemolytic Streptococcus</i>	≤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-susceptible” 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
Staphylococcus coagulase spp

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.

Other information

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

5.2 Pharmacokinetic propertiesAbsorption

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 cerebrospinal fluid

Levofloxacin has poor penetration into cerebrospinal fluid.

Penetration into prostatic tissue

After administration of oral 500mg 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, levofloxacin is eliminated relatively slowly from the plasma ($t_{1/2}$: 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, 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 dataAcute toxicity

The median lethal dose (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 p.o. 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 *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 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 (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:

Sodium stearyl fumarate,
Crospovidone,
Silica, colloidal anhydrous,
Copovidone,
Microcrystalline cellulose silicified (98% microcrystalline cellulose and 2% silica, colloidal)

Tablet coating:

Opadry II Pink (Lactose monohydrate, Hypromellose 15 cP, titanium dioxide (E171), triacetin, iron oxide red (E172), iron oxide yellow (E172)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Pack sizes:

Blister Al/PVC: 3, 5, 7, 10, 20, 50, 100 tablets

HDPE container with LDPE lid: 10, 50 and 100 tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf.
Reykjavíkurvegi 76-78
220 Hafnarfjörður
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/69/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 May 2010

10 DATE OF REVISION OF THE TEXT

September 2011