

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Levoxa 250 mg film-coated tablets
Levoxa 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet of Levoxa contains 250 mg of levofloxacin equivalent to 256.23 mg of levofloxacin hemihydrate

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

Excipient: lactose monohydrate.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Levoxa 250 mg film coated tablets

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.

Levoxa 500 mg film coated tablets

Pink biconvex tablets, scored on one side and marked with “L” on the other side.

Approximately 16 mm long and 8 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, Levoxa tablets are indicated for the treatment of the following infections when due to levofloxacin-susceptible microorganisms:

- Acute sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Urinary tract infections including pyelonephritis

- Chronic bacterial prostatitis.
- Skin and soft tissue infections.

Before prescribing Levoxa, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolone

4.2 Posology and method of administration

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 Levoxa 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

Levoxa 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. Levoxa 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 Levoxa:

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).

4.3 Contraindications

- hypersensitivity to levofloxacin or other quinolones or any of the excipients,
- epilepsy,
- history of tendon disorders related to fluoroquinolone administration,
- children or growing adolescents,
- pregnancy,
- breast-feeding women.

4.4 Special warnings and precautions for use

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

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

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 Levoxa. All patients should consult their physician immediately if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levoxa

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 Levoxa tablets, may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Levoxa tablets must be stopped immediately and patients should be treated with supportive measures and specific therapy as appropriate without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

Levoxa tablets are 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).

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of Levoxa should be adjusted in patients with renal impairment.

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 Levoxa 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

Very rare cases of QT interval prolongation have been reported in patients taking fluoroquinolones, including levofloxacin.

Caution should be taken when using fluoroquinolones, including levofloxacin in patients with known risk factor for QT interval prolongation, i.e:

- elderly
 - uncorrected electrolyte imbalance (i.e hypokalemia, hypomagnesemia)
 - congenital long QT syndrome
 - cardiovascular diseases (i.e cardiac failure, myocardial infarction, bradycardia)
- concomitant use of drugs known to prolong the QT interval (i.e IA and III class antiarrhythmics, tricyclic antidepressants, neuroleptics, macrolides).

See sections 4.2, 4.5 and 4.9.

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).

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 (See section 4.8).

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

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 Levoxa 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 Levoxa tablet administration. No interaction was found with calcium carbonate.

Sucralfate

The bioavailability of Levoxa tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levoxa, it is best to administer sucralfate 2 hours after the Levoxa tablet administration.

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.

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 effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Cyclosporin

The half-life of cyclosporin 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

Meals

There is no clinically relevant interaction with food. Levoxa tablets may therefore be administered regardless of food intake.

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, neuroleptics, macrolides) see section 4.4.

Laboratory tests

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.

Other relevant information

Clinical pharmacology studies were carried out to investigate possible pharmacokinetic interactions between levofloxacin and commonly prescribed drugs. 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, warfarin.

4.6 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, Levoxa tablets must not be used in pregnant women.

Lactation

There is no information on whether levofloxacin is excreted in breast milk. Levoxa tablets must therefore not be used during breast-feeding. Other quinolones cross into breast milk in amounts that may affect the child even at therapeutic doses.

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 following undesirable effects have been observed during treatment with levofloxacin.

The following frequency rating has been used:

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 ($\leq 1/10,000$), including isolated reports

Infections and infestations

Uncommon: fungal overgrowth and proliferation of other resistant microorganisms

Blood and the lymphatic system disorders

Uncommon: eosinophilia, leukopenia.

Rare: neutropenia, thrombocytopenia.

Very rare: agranulocytosis.

Isolated cases: haemolytic anaemia, pancytopenia.

Immune system disorders

Very rare: Allergic reactions (angioedema, hypotension, anaphylactic-like shock,), allergic pneumonitis

Isolated cases: severe bullous eruptions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) and erythema exsudativum multiforme.

Muco-cutaneous, anaphylactic /-oid reactions may sometimes occur even after the first dose.

Nervous system disorders

Uncommon: headache, dizziness/vertigo, drowsiness, insomnia.

Rare: paraesthesia, tremor, anxiety, depression, psychotic reactions with self-endangering behaviour including suicidal ideation or acts, agitation, confusion, convulsion.

Very rare: sensory and sensorimotor peripheral neuropathy, visual and auditory disturbances, disturbances of taste and smell, hallucinations.

Cardiac disorders

Rare: tachycardia.

Very rare: shock (anaphylactic-like).

Isolated cases: QT-interval prolongation (see section 4.4 and 4.9)

Vascular disorders

Rare: hypotension.

Respiratory, thoracic and mediastinal disorders

Rare: bronchospasm / dyspnoea.

Gastrointestinal disorders

Common: nausea, diarrhoea.

Uncommon: anorexia, vomiting, abdominal pain, dyspepsia.

Rare: bloody diarrhoea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis.

Very rare: hypoglycaemia, particularly in diabetic patients.

Hepato-biliary disorders

Common: increase in liver enzymes (e.g. ALT / AST).

Uncommon: increase in bilirubin

Very rare: liver reactions such as hepatitis

Not known: severe liver injury, including cases with acute liver failure, have been reported with levofloxacin, primarily in patients with severe underlying diseases (e.g. septicemia).

Skin and subcutaneous tissue disorders

Uncommon: pruritus, rash.

Rare: urticaria,

Very rare: photosensitisation

Musculoskeletal, connective tissue and bone disorders

Rare: arthralgia, myalgia, tendon disorders incl. tendinitis (e.g. Achilles tendon), (see 4.4).

Very rare: tendon rupture (e.g. Achilles tendon); this undesirable effect may occur within 48 hours of starting treatment and may be bilateral. (see 4.4). Muscular weakness, which may be of special importance in patients with myasthenia gravis.

Isolated cases: rhabdomyolysis.

Renal and urinary disorders

Uncommon: increase in serum creatinine.

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

General disorders and administration site conditions

Uncommon: asthenia

Very rare: fever.

Other undesirable effects which have been associated with fluoroquinolone administration include:

Vascular disorders

Hypersensitivity vasculitis

Nervous system disorders

extra pyramidal symptoms and other disorders of muscular coordination,

General disorders and administration site conditions

Attacks of porphyria in patients with porphyria.

4.9 Overdose

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

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. 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: fluoroquinolone class, ATC code: J01MA12
Levofloxacin is a synthetic broad-spectrum antibacterial agent and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mode of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Breakpoints

The preliminary NCCLS (US National Committee on Clinical Laboratory Standards) recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are:

Susceptible ≤ 2 mg/L, resistant ≥ 8 mg/L.

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. Therefore, the information presented provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to levofloxacin or not. Only microorganisms relevant to the given clinical indications are presented here.

In vitro antibacterial spectrum - Category with European range of resistance where this is known to vary

Susceptible

Aerobic Gram-positive micro-organisms:

<i>Enterococcus faecalis</i> ¹	10-35%
<i>Staphylococcus aureus</i> ¹ methi-S	
<i>Staphylococcus coagulase negative</i> methi-S(1)	0-30%
<i>Staphylococcus saprophyticus</i>	
<i>Streptococci</i> , group C and G	
<i>Streptococcus agalactiae</i>	
<i>Streptococcus pneumoniae</i> ¹ peni-I/S/R	
<i>Streptococcus pyogenes</i> ¹	

Aerobic Gram-negative micro-organisms:

<i>Acinetobacter baumannii</i> ¹	40%
<i>Citrobacter freundii</i> ¹	7%
<i>Eikenella corrodens</i>	
<i>Enterobacter aerogenes</i>	30%
<i>Enterobacter agglomerans</i>	
<i>Enterobacter cloacae</i> ¹	7%

<i>Escherichia coli</i> ¹	0-20% ²
<i>Haemophilus influenzae</i> ¹ ampi-S/R	
<i>Haemophilus para-influenzae</i> ¹	
<i>Klebsiella oxytoca</i>	
<i>Klebsiella pneumoniae</i> ¹	<5-10%
<i>Moraxella catarrhalis</i> ¹ β+ / β-	
<i>Morganella morganii</i> ¹	5%
<i>Pasteurella multocida</i>	
<i>Proteus mirabilis</i> ¹	0-15%
<i>Proteus vulgaris</i>	
<i>Providencia rettgeri</i>	
<i>Providencia stuartii</i>	35%
<i>Pseudomonas aeruginosa</i> ¹	10-50%
<i>Serratia marcescens</i> ¹	7%

Anaerobic micro-organisms:

Bacteroides fragilis
Clostridium perfringens
Peptostreptococcus

Other micro-organisms:

*Chlamydia pneumoniae*¹
Chlamydia psittaci
Chlamydia trachomatis
*Legionella pneumophila*¹
*Mycoplasma pneumoniae*¹
Mycoplasma hominis
Ureaplasma urealyticum

Intermediately susceptible

Aerobic Gram-positive micro-organisms:

Staphylococcus hemolyticus methi-R

Aerobic Gram-negative micro-organisms:

Burkholderia cepacia

Anaerobic micro-organisms:

Bacteroides ovatus
Bacteroides thetaiotamicron
Bacteroides vulgatus
Clostridium difficile

Resistant

Aerobic Gram-positive micro-organisms

Staphylococcus aureus methi-R
Staphylococcus coagulase negative methi-R

¹ Clinical efficacy has been proven in clinical studies.

Other information

The main mechanism of resistance is due to a *gyr-A* mutation. *In vitro* there is a cross-resistance between levofloxacin and other fluoroquinolones.

Acquired resistance with levofloxacin has recently been documented in 1997:

- *Streptococcus pneumoniae* France $\leq 1\%$
- *Haemophilus influenzae*: rare.

Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Nosocomial infections due to *Pseudomonas 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 %. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 600 mg.

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 $\mu\text{g/g}$ and 10.8 $\mu\text{g/ml}$ 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 $\mu\text{g/g}$ 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 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.

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 ($t_{1/2}$: 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.

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 (LD₅₀) 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,
Colloidal silicon dioxide 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

24 months.

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 pack sizes with 1, 3, 5, 7, 10, 14, 50, 200 film-coated tablets.
HDPE container with LDPE lid pack sizes with 50 and 100 film-coated tablets.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.
Reykjavíkurvegur 76-78
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

250mg - MA628/00501
500mg - MA628/00502

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26-02-2008

10. DATE OF REVISION OF THE TEXT

27-09-2008