

## **SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE MEDICINAL PRODUCT**

SAFELEVO 500mg

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each film coated tablet contains

Levofloxacin hemihydrate

Equivalent to Levofloxacin USP 500 mg.

For Excipients, please refer section 6.1.

### **3. PHARMACEUTICAL FORM**

Levofloxacin Tablets 500 mg are Pink colored, caplet shaped, film coated tablets with break line on one side and plain surface on another side.

### **4. CLINICAL PARTICULARS**

#### **4.1 Therapeutic Indications**

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

- Acute bacterial sinusitis
- Acute bacterial exacerbations of chronic bronchitis
- Community acquired pneumonia
- Chronic bacterial prostatitis
- Uncomplicated urinary tract infections
- Complicated urinary tract infections
- Skin and soft tissue infections

#### **4.2 Posology and Method of Administration**

Levofloxacin tablets are administered once or twice daily.

#### **Treatment time**

The duration of therapy varies according to the course of the disease (see below table)

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 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 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 > 50ml/min)*

Indication	Daily dose regimen (Depending on severity)	Duration of the treatment
Acute bacterial sinusitis	500 mg once daily	10-14 days
Acute bacterial 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

### **Special populations**

#### *Impaired renal function (creatinine clearance $\leq$ 50 ml/min)*

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

<sup>1</sup> No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)

#### *Impaired hepatic function*

No adjustment of dosage is required since Levofloxacin 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 imposed by consideration of renal function (see Section 4.4 QT interval prolongation).

#### *In children*

Levofloxacin is contraindicated in children and growing adolescents (less than 18 years of age) see Section 4.3.

**Legal Category: POM**

### 4.3 Contraindications

Levofloxacin tablets must not be used:

- in patients hypersensitive to levofloxacin, or to 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 (up to age of 18)
- 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 (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 on 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 (eg. 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 tablets may be symptomatic of Clostridium difficile-associated disease, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, Evoxil tablets must be stopped immediately, and patients should be treated with supportive measures and specific therapy without delay (e.g. oral metronidazole or 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 preexisting central nervous system damage; concomitant treatment with fenbufen and similar nonsteroidal anti-inflammatory drugs or with drugs which lower the cerebral seizure threshold, such as theophylline (see 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.

### **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 artificial UV rays (e.g. sunray lamp or 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 Evoxil 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 case 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 a history of psychiatric disease.

### **Cardiac disorders**

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

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia) - elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

(See section 4.2, section 4.5, section 4.8, section 4.9)

### **Peripheral neuropathy**

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should

be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

### **Opiates**

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific 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.

This medicinal product contains the colouring agent opadry II yellow 31K82672, which may cause allergic reactions.

## **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, buffered formulations or magnesium- or aluminium-containing antacids are administered concomitantly. It is recommended that preparations containing divalent or trivalent cations such as iron salts, buffered formulations or magnesium- or aluminium-containing antacids should not be taken 2 hours before or after Evoxil tablet administration. No interaction was found with calcium carbonate.

#### *Sucralfate*

The bioavailability of Evoxil 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-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 renal 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

### *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 (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 QT interval prolongation).

## Other forms of interactions

### *Meals*

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

## **4.6 Pregnancy and Lactation**

### *Pregnancy*

The product is contraindicated during 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 section 4.3 and 5.3)

### *Lactation*

The product is contraindicated in breast-feeding women. 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 ( $\geq 1/10$ )

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

Uncommon ( $\geq 1/1,000, \leq 1/100$ )

Rare ( $\geq 1/10,000, \leq 1/1,000$ )

Very rare ( $\leq 1/10,000$ )

Not known (cannot be estimated from the available data).

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

<i>Cardiac disorders</i>	
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)
<i>Blood and lymphatic system disorders</i>	
Uncommon	Leukopenia, eosinophilia
Rare	Thrombocytopenia, neutropenia
Very rare	Agranulocytosis
Not known	Pancytopenia, haemolytic anaemia
<i>Nervous system disorders</i>	
Uncommon	Dizziness, headache, somnolence
Rare	Convulsion, tremor, paraesthesia
Very rare	Sensory or sensorimotor peripheral neuropathy, dysgeusia including ageusia, parosmia including anosmia
<i>Eye disorders</i>	
Very rare	Visual disturbances
<i>Ear and labyrinth disorders</i>	
Uncommon	Vertigo

Very rare	Hearing impaired
Not known	Tinnitus

*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

*Renal and urinary disorders*

Uncommon	Blood creatinine increased
Very rare	Renal failure acute (e.g. due to nephritis interstitial)

*Skin and subcutaneous tissue disorders*

Uncommon	Rash, pruritis
Rare	Urticaria
Very rare	Angioneurotic oedema, photosensitivity reaction

Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, hyperhidrosis. Mucocutaneous reactions may sometimes occur even after the first dose.
<i>Musculoskeletal and connective tissue disorders</i>	
Rare	Tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), arthralgia, myalgia
Very rare	Tendon rupture (see section 4.4). This undesirable effect may occur within 48 hours of starting treatment and may be bilateral, muscular weakness which may be of special importance in patients with myasthenia gravis

Not known	Rhabdomyolysis
<i>Metabolism and nutrition disorders</i>	
Uncommon	Anorexia
Very rare	Hypoglycaemia, particularly in diabetic patients (see section 4.4)
<i>Infections and infestations</i>	
Uncommon	Fungal infection (and proliferation of other resistant microorganisms)
<i>Vascular disorders</i>	
Rare	Hypotension
<i>General disorders and administration site conditions</i>	
Uncommon	Asthenia
Very rare	Pyrexia
Not known	Pain (including pain in back, chest and extremities)

<i>Immune system disorders</i>	
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)
<i>Hepatobiliary disorders</i>	
Common	Hepatic enzyme increased (ALT/AST, alkaline phosphatase. CGT)
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).
<i>Psychiatric disorders</i>	
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), hallucinations

Other undesirable effects which have been associated with fluoroquinolones 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 supratherapeutic doses, the most important signs to be expected following acute overdosage of levofloxacin are central nervous symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in 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 Pharmacodynamics Properties

Pharmacotherapeutic group : Antiinfectives for systemic use - Antibacterials for systemic use - Quinolone antibacterials - Fluoroquinolones

ATC code : J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enantiomer of the racemic drug substance ofloxacin. 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> <sup>1</sup>	≤ 2mg/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> <sup>2</sup>	≤1 mg/L	>1 mg/L
Non-species related breakpoints <sup>3</sup>	≤ 1 mg/L	>2 mg/L

<sup>3</sup>Non-species related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distribution 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*, Gramnegative anaerobes).

### **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*<sup>§</sup>

*Eikebella corrodens*

*Haemophilus influenzae*\*

*Haemophilus para-influenza*\*

*Klebsiella oxytoca*

*Klebsiella pneumoniae*\*

*Moraxella catarrhalis*\* *Pasteurella multocida* *Proteus vulgaris*

<sup>1</sup> 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.

<sup>2</sup> 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.

*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**

*Enerococcus faecalis*\*

*Staphylococcus aureus methicillin-resistant*

*Staphylococcus haemolyticus methicillin-resistant*

**Aerobic Gram-negative bacteria**

*Acinetobacter baumannii*\*

*Citrobacter freundii*\*

*Enterobacter aerogenes*

*Enterbacter agglomerans*

*Enterobacter cloacae Escherichia coli\* Morganella morganii Proteus mirabilis\* Providencia stuartii*

*Pseudomonas aeruginosa*\*

*Serratia marcescens*\*

**Anaerobic bacteria**

*Bacteroides fragilis*

*Bacteroides ovatus*<sup>§</sup>

*Bacteroides thetaiotamicton*<sup>§</sup>

*Bacteroides vulgatus*<sup>§</sup>

*Clostridium difficile*<sup>§</sup>

\*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications

<sup>§</sup>Natural intermediate susceptibility

*Other information*

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

**5.2 Pharmacokinetic Properties**

**Absorption**

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1h. The absolute bioavailability is approximately 100%. Food has little effect on the absorption of levofloxacin.

**Distribution**

Approximately 30 - 40% of levofloxacin is bound to serum protein. 500 mg once daily multiple dosing with levofloxacin showed negligible accumulation. There is modest but predictable

accumulation of levofloxacin after doses of 500 mg twice daily. Steady-state is achieved within 3 days.

#### Penetration into tissues and body fluids:

##### *Penetration into Bronchial Mucosa, Epithelial Lining Fluid (ELF)*

Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after 500 mg p.o. were 8.3 µg/g and 10.8 µg/ml respectively. These were reached approximately one hour after administration.

##### *Penetration into Lung Tissue*

Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 µg/g and were reached between 4 and 6 hours after administration. The concentrations in the lungs consistently exceeded those in plasma.

##### *Penetration into Blister Fluid*

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

##### *Penetration into Cerebro-Spinal Fluid*

Levofloxacin has poor penetration into cerebro-spinal fluid.

##### *Penetration into Prostatic Tissue*

After administration of oral 500 mg levofloxacin once a day for three days, the mean concentrations in prostatic tissue were 8.7 µg/g, 8.2 µg/g and 2.0 µg/g, respectively after 2 hours, 6 hours and 24 hours; the mean prostate/plasma concentration ratio was 1.84.

##### *Concentration in Urine*

The mean urine concentrations 8 - 12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively.

#### **Biotransformation**

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5% of the dose excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

#### **Elimination**

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ( $t_{1/2}$ : 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.

#### Linearity

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

#### **Patients 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 <sub>cr</sub> [ml/min]	<20	20 - 40	50 - 80
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Cl <sub>R</sub> [ml/min]	13	26	57
t <sub>1/2</sub> [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 analysis for male and female subjects showed a small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

## **5.3 Preclinical Safety Data**

### **Acute toxicity**

The median lethal dose (LD<sub>50</sub>) 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 or 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 Effects 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**

Levofloxacin Tablets 500 mg:

Microcrystalline cellulose PH 101, crospovidone, Hydroxy propyl methyl cellulose, magnesium Stearate, Titanium dioxide and Iron oxide red.

### **6.2 Incompatibilities**

None.

### **6.3 Shelf Life**

36 months.

### **6.4 Special Precautions for Storage**

Do not store above 30°C, Protect from light and moisture.

### **6.5 Nature and Contents of Container:**

10 tablets of Safelevo 500 are sealed with PVC/PVDC on one side and printed aluminum on the other side in the form blister pack and 3 such 3 blisters are further packed in a carton along with instructions for use.

### **6.6 Special Precautions for Disposal**

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

## **7. MARKETING AUTHORISATION HOLDER**

### **MSN LABORATORIES PRIVATE LIMITED**

MSN House, Plot No.: C-24, Industrial Estate, Sanath Nagar, Hyderabad – 500 018 India.

## **8. MARKETING AUTHORISATION NUMBER**

0301/RWANDA FDA/2019

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

First Authorization: 12 March 2019

## **10. DATE OF REVISION OF THE TEXT**

April 2019