Summary of Product Characteristics

## 1.0 Name of the Medicinal Product

Levoxin Tablet 750 mg

## 2.0 Qualitative and Quantitative Composition

Each film coated tablet contains: Levofloxacin Hemihydrate USP eq to Levofloxacin ……750 mg

Excipients ……q.s

Approved colour used

For full list of excipients, see section 6.1

## 3.0 Pharmaceutical Form

Solid oral dosage form, Film Coated Tablet

White to off-white color, oblong shaped film coated tablets, engraved break line on one side & plain on other side.

## 4.0 Clinical Particulars

### 4.1 Therapeutic indications

Levofloxacin Tablets is indicated in adults for the treatment of the following infections

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections

For the above-mentioned infections Levofloxacin Tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

- Pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis

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- Uncomplicated cystitis
- Inhalation Anthrax: postexposure prophylaxis and curative treatment

Levofloxacin Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.

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

**4.2 Posology and method of administration**

Posology

Adults

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

Treatment time

The duration of therapy varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin Tablets should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Special populations

Geriatric patients

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

Renal and hepatic impairment

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

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| Indication | Daily dose regimen (according to severity) | Duration of treatment (according to severity) |
|---|---|---|
| Acute bacterial sinusitis | 500 mg once daily | 10 - 14 days |
| Acute bacterial exacerbations of chronic bronchitis | 500 mg once daily | 7 - 10 days |
| Community-acquired pneumonia | 500 mg once or twice daily | 7 - 14 days |
| Pyelonephritis | 500 mg once daily | 7 - 10 days |
| Complicated urinary tract | 500 mg once daily | 7 - 14 days |
| infections | | |
| Uncomplicated cystitis | 250 mg once daily | 3 days |
| Chronic bacterial prostatitis | 500 mg once daily | 28 days |
| Complicated Skin and soft tissue infections | 500 mg once or twice daily | 7 - 14 days |
| Inhalation Anthrax | 500 mg once daily | 8 weeks |

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Impaired renal function (creatinine clearance ≤ 50 ml/min)

| Creatinine clearance | Dosage regimen | | |
|---|---|---|---|
| | 250 mg/24 h | 500 mg/24 h | 500 mg/12 h |
| | First dose: 250 mg | First dose: 500 mg | First dose: 500 mg |
| 50-20 ml/min | Then:125 mg/24h | 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).

Impaired liver function

No adjustment of dosage is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys

Pediatric population

Levofloxacin is contraindicated in children and growing adolescents.

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 dose. The tablets may be taken during meals or between meals. Levofloxacin Tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents), and sucralfate administration since reduction of absorption can occur.

**4.3 Contraindications**

Levofloxacin Tablets must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or to any of the excipients listed in section 6.1,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,

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- in children or growing adolescents
- during pregnancy,
- in breast-feeding women.

**4.4 Special warnings and precautions for use**

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 (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Bronchitis when these infections have been adequately diagnosed.

Resistance to fluoroquinolones of E. coli – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in E. coli to fluoroquinolones.

Inhalation Anthrax: Use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. The daily dose should be adjusted in

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elderly patients based on creatinine clearance. Close monitoring of these patients is therefore necessary if they are prescribed Levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, Levofloxacin Tablets should be stopped immediately and appropriate treatment initiated without delay (e.g. oral metronidazole or vancomycin). Medicinal products inhibiting the peristalsis are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

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. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

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

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema to anaphylactic shock), occasionally following the initial dose. Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia

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

Prevention of photosensitisation

Photosensitisation has been reported 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), during treatment and for 48 hours following treatment discontinuation 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

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antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

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. 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.

QT interval prolongation

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

- congenital long QT syndrome

-concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)

- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

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.

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Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with 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 method. Levofloxacin may inhibit the growth of Mycobacterium tuberculosis and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

**4.5 Interaction with other medicinal products and other forms of interaction**

<u>Effect of other medicinal products on levofloxacin</u>

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Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminiumcontaining antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with Levofloxacin Tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken 2 hours before or after Levofloxacin Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

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

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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.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs:

- calcium carbonate
- digoxin - glibenclamide - ranitidine.

Effect of levofloxacin on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33 % when coadministered with levofloxacin.

Vitamin K antagonists

Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.

Drugs known to prolong the 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, antipsychotic).

Other relevant information

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

Other forms of interactions

Meals

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

**4.6 Fertility, pregnancy and lactation**

Pregnancy:

There are limited amount of data with respect to the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women.

Breast-feeding

Levofloxacin tablets are contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women. Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

**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).

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## 4.8 Undesirable effects

a. Summary of Safety profile

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies are defined using the following convention: very common (≥ 1/10), common (≥

1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

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

b. Tabulated summary of adverse reactions

| System organ class | Common (≥1/100 to <1/10 ) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Not known (cannot be estimated from available data) |
|---|---|---|---|---|
| Infections and infestations | | Fungal infection including Candida infection<br>Pathogen resistance | | |
| Blood and lymphatic system disorders | | Leukopenia<br>Eosinophilia | Thrombocytopenia<br>Neutropenia | Pancytopenia<br>Agranulocytosis<br>Haemolytic anaemia |
| Immune system disorders | | | Angioedema<br>Hypersensitivity | Anaphylactic shock[a]<br>Anaphylactoid shock[a] |

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| | | | | |
|---|---|---|---|---|
| Metabolism and nutrition disorders | | Anorexia | Hypoglycaemia particularly in diabetic patients | Hyperglycaemia<br>Hypoglycaemic coma |
| Psychiatric disorders | Insomnia | Anxiety<br>Confusional state<br>Nervousness | Psychotic reactions (with e.g. hallucination, | Psychotic disorders with self-endangering behaviour including |

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| | | | | |
|---|---|---|---|---|
| | | | paranoia)<br>Depression<br>Agitation<br>Abnormal dreams<br>Nightmares | suicidal ideation or suicide attempt |
| Nervous system disorders | Headache<br>Dizziness | Somnolence<br>Tremor<br>Dysgeusia | Convulsion<br>Paraesthesia | Peripheral sensory neuropathy<br>Peripheral sensory motor neuropathy<br>Parosmia including anosmia Dyskinesia<br>Extrapyramidal disorder<br>Ageusia<br>Syncope<br>Benign intracranial hypertension |
| Eye disorders | | | Visual disturbances such as blurred<br>vision | Transient vision loss |
| Ear and Labyrinth disorders | | Vertigo | Tinnitus | Hearing loss<br>Hearing impaired |

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| | | | | |
|---|---|---|---|---|
| Cardiac disorders | | | Tachycardia,<br>Palpitation | Ventricular tachycardia, which may result in cardiac arrest<br>Ventricular arrhythmia and torsade de pointes<br>(reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged |
| Vascular disorders | | | Hypotension | |
| Respiratory, thoracic and mediastinal disorders | | Dyspnoea | | Bronchospasm<br>Pneumonitis allergic |
| Gastro-intestinal disorders | Diarrhoea<br>Vomiting<br>Nausea | Abdominal pain<br>Dyspepsia<br>Flatulence<br>Constipation | | Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis<br>Pancreatitis |

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| | | | | |
|---|---|---|---|---|
| | | | | |
| Hepatobiliary disorders | Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT) | Blood bilirubin increased | | Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases Hepatitis |
| Skin and subcutaneous tissue disorders [b] | | Rash<br>Pruritus<br>Urticaria<br>Hyperhidrosis | | Toxic epidermal necrolysis Stevens-Johnson syndrome<br>Erythema multiforme Photosensitivity reaction<br>Leukocytoclastic vasculitis<br>Stomatitis |

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| | | | | |
|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia | Tendon disorders including tendinitis<br>(e.g. Achilles tendon)<br>Muscular weakness which may be of special importance in patients with myasthenia gravis | Rhabdomyolysis<br>Tendon rupture (e.g. Achilles tendon)<br>Ligament rupture<br>Muscle rupture<br>Arthritis |
| Renal and Urinary disorders | | Blood creatinine increased | Renal failure acute<br>(e.g. due to interstitial nephritis) | |
| General disorders and administration site conditions | | Asthenia | Pyrexia | Pain (including pain in back, chest, and extremities) |

Immune system disorders: allergic reaction (syncope, hypotension, dyspnea, urticaria). Skin and subcutaneous tissue disorders: blisters, discomfort/pain, oedema, erythema, irritation,

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peeling/exfoliation, pruritus, rash, stinging/burning.

c. Description of selected adverse reactions No information available.

d. Paediatric population No information available.

e. Other special population No information available.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via https://pv.pharmacyboardkenya.org

**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 levofloxacin are central nervous system 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.

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

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

## 5.0 Pharmacological Properties

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## 5.1 **Pharmacodynamic properties**

Pharmacotherapeutic group and ATC code:

Pharmacotherapeutic group: Antiifectives for systemic use – Antibacterials for systemic use –

Quinolone antibasterials – Fluoroquinolones

ATC code: J01MA12

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(s) of resisance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. 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 (version 2.0, 2012-01-01):

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| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacteriacae | ≤1 mg/L | >2 mg/L |
| Pseudomonas spp. | ≤1 mg/L | >2 mg/L |
| Acinetobacter spp. | ≤1 mg/L | >2 mg/L |
| Staphylococcus spp. | ≤1 mg/L | >2 mg/L |
| S.pneumoniae [1] | ≤2 mg/L | >2 mg/L |
| Streptococcus A,B,C,G | ≤1 mg/L | >2 mg/L |
| H.influenzae[2, 3] M.catarrhalis [3] | ≤1 mg/L | >1 mg/L |
| Non-species related breakpoints [4] | ≤1 mg/L | >2 mg/L |

H. influenzae.

3. Strains with MIC values above the susceptible 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 must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

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

1 . The breakpoints for levofloxacin relate to high dose therapy.

2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with

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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 |
| Bacillus anthracis<br>Staphylococcus aureus methicillin-susceptible<br>Staphylococcus saprophyticus<br>Streptococci, group C and G<br>Streptococcus agalactiae<br>Streptococcus pneumoniae<br>Streptococcus pyogenes |
| Aerobic Gram- negative bacteria |
| Eikenella corrodens<br>Haemophilus influenzae<br>Haemophilus para-influenzae<br>Klebsiella oxytoca<br>Moraxella catarrhalis<br>Pasteurella multocida |

| |
|---|
| Proteus vulgaris<br>Providencia rettgeri |
| Anaerobic bacteria |
| Peptostreptococcus |
| Other |

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| |
|---|
| Chlamydophila pneumoniae<br>Chlamydophila psittaci<br>Chlamydia trachomatis<br>Legionella pneumophila<br>Mycoplasma pneumoniae<br>Mycoplasma hominis<br>Ureaplasma urealyticum |
| Species for which acquired resistance may be a problem |
| Aerobic Gram-positive bacteria |
| Enterococcus faecalis<br>Staphylococcus aureus methicillin-resistant[#]<br>Coagulase negative Staphylococcus spp |
| Aerobic Gram- negative bacteria |
| Acinetobacter baumannii<br>Citrobacter freundii<br>Enterobacter aerogenes<br>Enterobacter cloacae<br>Escherichia coli<br>Klebsiella pneumoniae<br>Morganella morganii<br>Proteus mirabilis<br>Providencia stuartii |
| Pseudomonas aeruginosa<br>Serratia marcescens |

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| |
|---|
| Anaerobic bacteria |
| Bacteroides fragilis |
| Inherently resistant Strains |
| Aerobic Gram-positive bacteria |
| Enterococcus faecium |

# Methicillin-resistant S. aureus are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

**5.2 Pharmacokinetic properties:**

Absorption

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1- 2 h. The absolute bioavailability is 99- 100 %.

Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

Distribution

Approximately 30 - 40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

Biotransformation

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

Elimination

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma ($t_{½}$: 6 - 8 h). Excretion is primarily by the renal route > 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.

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 1000 mg.

Special populations

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:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

| | | | |
|---|---|---|---|
| $Cl_{cr}$ [ml/min] | < 20 | 20 - 49 | 50 - 80 |
| $Cl_R$ [ml/min] | 13 | 26 | 57 |
| $t_{1/2}$ [h] | 35 | 27 | 9 |

Elderly subjects

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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:**

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse 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 photocarcinogenity study.

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.

**6.0 Pharmaceutical Particulars**

**6.1 List of excipients**

Microcrystalline cellulose (102)

Crospovidone USP

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Croscarmellose Sodium USP

Hydroxypropyl methyl cellulose 6cps

Magnesium Stearate

Opadry II White

Purified Water

**6.2 Incompatibilities**

Not applicable

**6.3 Shelf life**

24 months.

**6.4 Special precautions for storage**

Store below 30°C.

**6.5 Nature and contents of container**

Alu-PVC blister pack of 2 x S's tablets. Each blister is packed in printed carton with the product name and batch details along with the information of the manufacturer

**6.6 Special precautions for disposal and other handling**

No special requirement

**7.0 Marketing Authorization Holder and Manufacturing Site Addresses**

Marketing Authorization Holder:

Company Name: THE SEARLE COMPANY LIMITED

**8.0 Marketing Authorization Number**

H2022/CTD7874/15061

**9.0 Date of First Registration/Renewal of the Registration**

13/01/2022

**10.0 Date of Revision of the Text**

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13/01/2022

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