**SUMMARY OF PRODUCT CHARACTERISTICS (SPC)**

## 1. NAME OF THE MEDICINAL PRODUCT

NARAFLOX (LEVOFLOXACIN TABLETS USP 500 MG)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Batch size: 1,12,000 tablets

| Sr no. | L.C. per tablet (mg) | Ove (%) | Ingredients | Specifications | Unit | A.Q.R/B In Kg |
|---|---|---|---|---|---|---|
| **MIXING** | | | | | | |
| 1. | 500 | - | Levofloxacin (B)* | USP | Kg | 56.00 |
| 2. | 26.800 | - | Microcrystalline cellulose powder | BP | Kg | 3.002 |
| 3. | 20.00 | - | Crospovidone (Kollidon) | BP | Kg | 2.240 |
| **BINDING** | | | | | | |
| 4. | 10.00 | - | Povidone (K-30) | BP | Kg | 1.120 |
| 5. | Q. S | - | Purified water | BP | Kg | Q. S |
| **LUBRICANTS** | | | | | | |
| 4. | 6.200 | - | Magnesium stearate | BP | Kg | 0.694 |
| 5. | 12.000 | - | Sodium stearyl fumarate | BP | Kg | 1.344 |
| 6. | 15.000 | - | Crospovidone (Kollidon) | BP | Kg | 1.680 |
| 7. | 10.000 | - | Microcrystalline cellulose powder | BP | Kg | 1.120 |
| **COATING** | | | | | | |
| 8. | 18.00 | - | Sunset yellow aqu. Coat readymix | IHS | gm | 2016.00 |
| 9. | Q. S | - | Purified water | BP | Kg | Q. S |
| | **618 MG** | | **Total weight** | | | **69.2160** |

(B)* = Quantity to be calculated on the basis of its potency

(D) $ = Quantity to be compensated on increasing quantity of active material and its L.O.D

**A.Q.R/B** = Actual Quantity Required Per Batch

**Ove %** = Overages in %

**L.C per Tablet** = Label claim per tablet

**IHS** = In house specification

**BP** = British pharmacopoeia

**USP** = United States Pharmacopoeia

Weight of compressed tablet: 618 mg

## 3. PHARMACEUTICAL FORM

Film coated tablet

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

- Acute bacterial sinusitis
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis Uncomplicated cystitis.
- 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.
- Acute pyelonephritis and complicated urinary tract infections Chronic bacterial prostatitis
- 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

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. 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.

The following dose recommendations can be given for Levofloxacin Tablets:

*Dosage in patients with normal renal function*

*(creatinine clearance > 50 ml/min)*

| **Indication** | **Daily dose regimen (According to severity)** | **Duration of treatment** *(According to severity)* |
|---|---|---|
| Acute bacterial sinusitis | 500 mg once daily | 10 - 14 days |
| Acute exacerbations of chronic obstructive pulmonary disease including bronchitis | 500 mg once daily | 7 - 10 days |
| Community-acquired pneumonia | 500 mg once or twice daily | 7 - 14 days |
| Acute pyelonephritis | 500 mg once daily | 7 - 10 days |
| Complicated urinary tract infections | 500 mg once daily | 7 - 14 days |
| 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 |

*Special Populations*

***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.

*Elderly population*

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

*Paediatric 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 used in the formulation.
- In patients with epilepsy,
- In patients with history of tendon disorders related to fluoroquinolone administration,
- In children or growing adolescents
- During pregnancy,
- In breast-feeding women.

## 4.4 Special warnings and precautions for use

The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with Levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones, Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

For both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally

- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally

- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

*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 and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with

corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. The daily dose should be adjusted in elderly patients based on creatinine clearance.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

*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*

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 cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin. At the time of prescription, patients should be advised

of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

*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 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.

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

*Effect of other medicinal products on levofloxacin*

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

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing 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 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*

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 Pregnancy and lactation

*Pregnancy*

There is 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).

## 4.8 Undesirable effects

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.

| **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 |
| 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, paranoia)<br>Depression<br>Agitation<br>Abnormal dreams<br>Nightmares | Psychotic disorders with self-endangering behaviour including 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<br>Dyskinesia<br>Extrapyramidal disorder<br>Ageusia<br>Syncope |

| | | | | |
|---|---|---|---|---|
| | | | | Benign intracranial hypertension |
| Eye disorders* | | | Visual disturbances such as blurred vision | Transient vision loss |
| Ear and Labyrinth disorders* | | Vertigo | Tinnitus | Hearing loss<br>Hearing impaired |
| Cardiac disorders** | | | Tachycardia, Palpitation | Ventricular tachycardia, which may result in cardiac arrest<br>Ventricular arrhythmia and torsade de pointes (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 |
| 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<br>Hepatitis |
| Skin and subcutaneous tissue disorders [b] | | Rash<br>Pruritus<br>Urticaria<br>Hyperhidrosis | Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption | Toxic epidermal necrolysis<br>Stevens-Johnson syndrome<br>Erythema multiforme |

| | | | | |
|---|---|---|---|---|
| | | | | Photosensitivity reaction<br>Leukocytoclastic vasculitis<br>Stomatitis |
| Endocrine disorders | | | Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) | |
| Musculoskeletal and connective tissue disorders | | Arthralgia<br>Myalgia | Tendon disorders including tendinitis (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 (e.g. due to interstitial nephritis) | |
| General disorders and administration site conditions* | | Asthenia | Pyrexia | Pain (including pain in back, chest, and extremities) |

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

[b] Mucocutaneous reactions may sometimes occur even after the first dose

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

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

• attacks of porphyria in patients with porphyria.

## 4.9 Overdose

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.

## 5.1 Pharmacodynamic properties

### 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group:** Anti-infective for systemic use – Antibacterial for systemic use – Quinolone antibacterial – 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(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).

| **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 |

[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 *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 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 |

| |
|---|
| 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<br>Proteus vulgaris<br>Providencia rettgeri |
| **Anaerobic bacteria** |
| Peptostreptococcus |
| **Other** |
| 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<br>Pseudomonas aeruginosa<br>Serratia marcescens |
| **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

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 ($t_{½}$: 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

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. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

- Microcrystalline cellulose powder BP
- Crospovidone (Kollidon) BP
- Povidone (K-30) BP
- Purified water BP
- Magnesium stearate BP
- Sodium stearyl fumarate USP
- Sunset yellow aq. Coat readymix IHS

### 6.2 Incompatibilities

Not known.

### 6.3 Shelf life

36 months

### 6.4 Special precautions for storage

Store at a temperature not exceeding 30℃ in a dry place. Protect from light.

### 6.5 Nature and contents of container

10 x 1 x 10 Alu/ Alu pack.

### 6.6 Special precautions for disposal and other handling

None.

## 7. Applicant/ Manufacturer

MANUFACTURER BY:

Name: BAROQUE PHARMACEUTICALS PVT LTD.,

Address: 192/2 & 3, 190/1 and 202/9, SOKHADA-388620,

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