**Summary of Product Characteristics for Pharmaceutical Products**

## 1. Name of the medicinal product

Leflox Tablets 500mg

## 2. Qualitative and quantitative composition

Each film-coated tablet contains:
Levofloxacin USP ... 500 mg

For a full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Cream coloured, oblong shaped film coated tablets, engraved "GETZ" on one side and "LF|500" on the other.

## 4. Clinical particulars

### 4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions, this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection;
- other first-line antibiotics are contraindicated in an individual patient;
- other first-line antibiotics have caused side effects requiring treatment to be stopped;
- treatment with other first-line antibiotics has failed.

In adults, Leflox Tablets are indicated for the treatment of the following infections:

- Acute bacterial sinusitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections / complicated skin and skin structure infection
- Acute pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis
- Uncomplicated cystitis
- Inhalation Anthrax: postexposure prophylaxis and curative treatment
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis

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

Leflox 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.

Leflox Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin; given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

The following dose recommendations can be given for Levofloxacin:

| **Indication** | **Daily dose regimen (according to severity)** | **Duration of treatment** |
|---|---|---|
| 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 |
| Uncomplicated cystitis | 250 mg once daily | 3 days |
| Complicated urinary tract infections | 500 mg once daily | 7 – 14 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).

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

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 (less than 18 years of age).

***Method of administration***
Leflox Tablets should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals. Leflox 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,
- in children or growing adolescents,
- during pregnancy,
- in breast-feeding women

## 4.4 Special warnings and precautions for use
The use of Levofloxacin Tablets 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 tablets should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

***Prolonged, disabling and potentially irreversible serious adverse drug reactions***
Very rare cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Levofloxacin Tablet should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

***Risk of resistance***
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 regions. 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 levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendonitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, in patients receiving daily doses of 1000 mg levofloxacin and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) treatment with Levofloxacin tablet 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.

***Myoclonus***
Cases of myoclonus have been reported in patients receiving levofloxacin. The risk is increased in older patients, and in patients with renal impairment if the dose of levofloxacin is not adjusted as per the creatinine clearance. Levofloxacin should be discontinued immediately at the first occurrence of myoclonus and appropriate treatment should be initiated.

**Clostridium difficile-associated disease**
Diarrhoea, particularly if severe, persistent and / or bloody, during or after treatment with Levofloxacin tablets (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 must be stopped immediately and appropriate treatment initiated without delay (e.g. oral vancomycin). 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 tablets are contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to, or concomitant treatment with drugs which 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, and so levofloxacin should be used with caution. 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 up 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.

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

***Prevention of photosensitisation***
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), 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 tablets 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 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)
• Elderly patients and women may be more sensitive to QTc-prolonging medications.
• cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).
Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

***Peripheral neuropathy***
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving fluoroquinolones. Patients under treatment with Levofloxacin Tablets should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition.

***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. 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.

***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 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 vascular 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.

***Acute pancreatitis***
Acute pancreatitis may be observed in patients taking levofloxacin. Patients should be informed of the characteristic symptoms of acute pancreatitis. Patients experiencing nausea, malaise, abdominal discomfort, acute abdominal pain or vomiting should have a prompt medical evaluation. If acute pancreatitis is suspected, levofloxacin should be discontinued; if confirmed, levofloxacin should not be restarted. Caution should be exercised in patients with a history of pancreatitis.

***Blood disorders***
Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin. If any of these blood disorders is suspected, blood counts should be monitored. In case of abnormal results, discontinuation of treatment with levofloxacin should be considered.

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

**Effect of other medicinal products on Levofloxacin Tablets:**

*Iron 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 tablet 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, it is best to administer sucralfate 2 hours after the Levofloxacin tablet administration.

*Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs*
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.
Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

*Probenecid and cimetidine*
Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.
Caution should be exercised when levofloxacin is coadministered with drugs that 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 Tablets 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 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).

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**

*Food*
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 is limited amount of data from 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 the experimental data suggesting a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets must not be used in pregnant women.

*Breast-feeding*
Levofloxacin is 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 the experimental data suggesting a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin tablets 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

[Effects on ability to drive and use machines – not usable from source: the corresponding text in the source document was corrupted by a copy-paste of the section 4.6 fertility statement and did not describe any actual effect on driving/machine use. To be confirmed and supplied by the Marketing Authorisation Holder.]

## 4.8 Undesirable effects

| **Infections and Infestations** | |
|---|---|
| Fungal infection including Candida infection | Uncommon |
| Pathogen resistance | Uncommon |
| **Blood and lymphatic system disorders** | |
| Leukopenia | Uncommon |

| | |
|---|---|
| Eosinophilia | Uncommon |
| Thrombocytopenia | Rare |
| Neutropenia | Rare |
| Bone marrow failure including aplastic anaemia, pancytopenia, agranulocytosis, haemolytic anaemia | Not known |
| **Immune system disorders** | |
| Angioedema | Rare |
| Hypersensitivity | Rare |
| Anaphylactic shock | Not known |
| Anaphylactoid shock | Not known |
| **Metabolism and nutrition disorders** | |
| Anorexia | Uncommon |
| Hypoglycaemia particularly in diabetic patients | Rare |
| Hypoglycaemic coma | Rare |
| Hyperglycaemia | Not known |
| **Psychiatric disorders** | |
| Insomnia | Common |
| Anxiety | Uncommon |
| Confusional state | Uncommon |
| Nervousness | Uncommon |
| Psychotic reactions (with e.g. hallucination, paranoia) | Rare |
| Depression | Rare |
| Agitation | Rare |
| Abnormal dreams | Rare |
| Nightmares | Rare |
| Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt | Not known |
| Mania | Not known |
| **Nervous system disorders** | |
| Headache | Common |
| Dizziness | Common |
| Somnolence | Uncommon |
| Tremor | Uncommon |
| Dysgeusia | Uncommon |
| Paraesthesia | Rare |
| Convulsion | Rare |
| Memory impairment | Rare |
| Peripheral sensory neuropathy | Rare |
| Peripheral sensory motor neuropathy | Rare |
| Parosmia including anosmia | Rare |
| Dyskinesia | Rare |
| Extrapyramidal disorder | Rare |
| Ageusia | Rare |
| Syncope | Rare |
| Benign intracranial hypertension | Rare |
| Myoclonus | Rare |
| **Eye disorders** | |
| Visual disturbances such as blurred vision | Rare |
| Transient vision loss | Not known |
| Uveitis | Not known |
| **Ear and labyrinth disorders** | |
| Vertigo | Uncommon |
| Tinnitus | Rare |
| Hearing loss | Not known |
| Hearing impaired | Not known |

| | |
|---|---|
| **Cardiac disorders** | |
| Tachycardia | Rare |
| Palpitation | Rare |
| Ventricular tachycardia which may result in cardiac arrest | Not known |
| Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation) | Not known |
| Electrocardiogram QT prolonged | Not known |
| **Vascular disorders** | |
| Hypotension | Rare |
| **Respiratory, thoracic and mediastinal disorders** | |
| Dyspnoea | Uncommon |
| Bronchospasm | Not known |
| Pneumonitis allergic | Not known |
| **Gastrointestinal disorders** | |
| Diarrhoea | Common |
| Vomiting | Common |
| Nausea | Common |
| Abdominal pain | Uncommon |
| Dyspepsia | Uncommon |
| Flatulence | Uncommon |
| Constipation | Uncommon |
| Pancreatitis | Not known |
| Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis | Not known |
| **Hepatobiliary disorders** | |
| Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT) | Common |
| Blood bilirubin increased | Uncommon |
| Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases | Not known |
| Hepatitis | Not known |
| **Skin and subcutaneous tissue disorders** | |
| Rash | Uncommon |
| Pruritus | Uncommon |
| Urticaria | Uncommon |
| Hyperhidrosis | Uncommon |
| Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) | Rare |
| Fixed drug eruption | Rare |
| Toxic epidermal necrolysis | Not known |
| Stevens-Johnson syndrome | Not known |
| Erythema multiforme | Not known |
| Photosensitivity reaction | Not known |
| Leukocytoclastic vasculitis | Not known |
| Stomatitis | Not known |
| Skin hyperpigmentation | Not known |
| **Musculoskeletal and connective tissue disorders** | |
| Arthralgia | Uncommon |
| Myalgia | Uncommon |
| Tendon disorders including tendinitis (e.g. Achilles tendon) | Rare |
| Muscular weakness which may be of special importance in patients with myasthenia gravis | Rare |

| | |
|---|---|
| Tendon rupture (e.g. Achilles tendon) | Not known |
| Rhabdomyolysis | Not known |
| Ligament rupture | Not known |
| Muscle rupture | Not known |
| Arthritis | Not known |
| **Renal and urinary disorders** | |
| Blood creatinine increased | Uncommon |
| Renal failure acute (e.g. due to interstitial nephritis) | Rare |
| **General disorders and administration site conditions** | |
| Asthenia | Uncommon |
| Pyrexia | Rare |
| Pain (including pain in back, chest, and extremities) | Not known |
| **Endocrine disorders** | |
| Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) | Rare |

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) 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 tablets 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, myoclonus, 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. Pharmacological properties

## 5.1 Pharmacodynamic properties

**Pharmacotherapeutic group: Quinolone antibacterials - Fluoroquinolones**

**ATC-code: J01MA12**

***Mechanism of action***

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.
As a fluoroquinolone antibacterial agent, levofloxacin acts on the 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 (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

***Mechanism of resistance***
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.

## 5.2 Pharmacokinetic properties

***Absorption***
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 hr. The absolute bioavailability is approximately 99-100%.
Food has little effect on the absorption of levofloxacin. Steady state conditions are reached within 48 hours following a 500mg 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 500mg 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 into 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 (t1/2: 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 500mg 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 1000mg.

***Special populations***
**Subjects with renal impairment**
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 500mg dose

| **ClCr [ml/min]** | **< 20** | **20 – 49** | **50 – 80** |
|---|---|---|---|
| ClR [ml/min] | 13 | 26 | 57 |
| t1/2 [h] | 35 | 27 | 9 |

**Elderly subjects**
There are no significant differences in levofloxacin pharmacokinetics 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

Hydroxypropyl Methylcellulose (Pharmacoat 606)
Crospovidone
Microcrystalline Cellulose (Avicel PH-102)
Magnesium Stearate
Opadry II Yellow 85G32558

### 6.2 Incompatibilities

None.

### 6.3 Shelf life

5 Years
The expiration dates refer to the product correctly stored in the required conditions.

### 6.4 Special precautions for storage

Store below 30°C. Protect from sunlight and moisture. Keep out of reach of children.

### 6.5 Nature and contents of container

Leflox (Levofloxacin) Tablet 500mg are available in Alu-Alu Blister Pack of 1 x 10 (10's) tablets along with the package insert.

### 6.6 Special precautions for disposal and other handling

No special requirements for disposal.
To be sold on prescription of a registered medical practitioner only.
Keep out of reach of children.

## 7. Marketing authorisation holder

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area, Karachi 74900, Pakistan
Tel: (92-21) 111-111-511
Fax: (92-21) 5057592

## 8. Marketing authorisation number

H2010/15474/R1

## 9. Date of first authorisation/renewal of the authorisation

2nd March 2026

## 10. Date of revision of the text

26th August 2026