# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

Terlev-750 (Levofloxacin Tablets 750mg)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Film-coated tablet contains;

Levofloxacin Hemihydrate equivalent to Levofloxacin 750mg

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film coated tablets

Brownish pink colored, oblong shaped film-coated tablets with a break line on one surface.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) 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.

Levofloxacin tablets is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Acute pyelonephritis and complicated urinary tract infections (see section 4.4)
- Chronic bacterial prostatitis

- Inhalation Anthrax: postexposure prophylaxis and curative treatment (see section 4.4)
- Acute bacterial sinusitis
- Acute exacerbation of chronic obstructive pulmonary disease including bronchitis
- Community acquired pneumonia
- Complicated skin and soft tissue infections
- Uncomplicated cystitis (see section 4.4)

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

**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 susceptibility of the presumed causative pathogen.

Levofloxacin 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.

Posology

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 bacterial 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 ≤ 50ml/min)

| | **Dose regimen** | | |
|---|---|---|---|
| | **250 mg/24 h** | **500 mg/24 h** | **500 mg/12 h** |
| **Creatinine clearance** | *first dose:* 250 mg | *first dose:* 500 mg | *first dose:* 500 mg |
| 50-20 ml/min | *then:* 125 mg/24 h | *then:* 250 mg/24 h | *then:* 250 mg/12 h |
| 19-10 ml/min | *then:* 125 mg/48 h | *then:* 125 mg/24 h | *then:* 125 mg/12 h |
| <10 ml/min (including haemodialysis and CAPD) [1] | *then:* 125 mg/48 h | *then:* 125 mg/24 h | *then:* 125 mg/24 h |

[1] No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

*Impaired liver function*

No adjustment of dose 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 dose is required in the elderly, other than that imposed by consideration of renal function. (see section 4.4 “Tendinitis and tendon rupture” and “QT interval prolongation).

*Paediatric population*

Levofloxacin tablets is contraindicated in children and growing adolescents (see section 4.3).

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 (see section 4.5).

**4.3 Contraindications**

Levofloxacin tablets must not be used:

• in patients hypersensitive to levofloxacin or other quinolones or 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 breastfeeding women.

**4.4 Special warning and precautions**

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 (see section 4.8). Treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

*Risks 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 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.

*Prolonged, disabling and potentially irreversible serious adverse drug reactions*

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 tablets 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.

*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. The risk of tendinitis 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 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) 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.

*Myoclonus*

Cases of myoclonus have been reported in patients receiving levofloxacin (see section 4.8). The risk of myoclonus 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.

*Blood disorders*

Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin (see section 4.8). 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.

*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 (see section 4.8). 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 should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products 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 (see section 4.3) 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 (see section 4.5). In case of convulsive seizures (see section 4.8), 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 (see section 4.2).

*Hypersensitivity reactions*

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

*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 (see section 4.8). 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, occuring more frequently in the elderly, 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 (see section 4.8).

Levofloxacin tablets treatment should be stopped immediately if a patient reports blood glucose disturbance and alternative nonfluoroquinolone antibacterial therapy should be considered.

*Prevention of photosensitization*

Photosensitisation has been reported with levofloxacin (see section 4.8). 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 photosensitization.

*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. (see section 4.5).

*Psychotic reactions*

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice. Alternative nonfluoroquinolone antibacterial therapy should be considered, 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. hypokalaemia, hypomagnesaemia)
- 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 (See sections 4.2 Elderly, 4.5, 4.8 and 4.9.)

*Peripheral neuropathy*

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with levofloxacin 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. (see section 4.8).

*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 (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

*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 (see sections 4.7 and 4.8).

*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 (see section 4.8).

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 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 Sjogren'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.

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

Effect of other medicinal products on levofloxacin tablets

*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 (see section 4.2). 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 (see section 4.2).

*Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs*

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

*Probenecid and cimetidine*

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

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

*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 (see section 4.4).

*Drugs known to prolong QT interval*

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 QT interval prolongation)

*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 are 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 (see section 5.3). 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 (see sections 4.3 and 5.3)

Breastfeeding

Levofloxacin tablets 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 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 (see sections 4.3 and 5.3).

Fertility

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

**4.7 Effects on ability to drive and use machine:**

Levofloxacin tablets has minor or moderate influence on the ability to drive and use machines. Some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

**4.8 Undesirable effects:**

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

Frequencies in this table are defined using the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, < 1/100), rare (≥1/10000, < 1/1000), very rare (<1/10000), not known (cannot be estimated from the available data).

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

Table 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 Pathogen resistance | | |
| Blood and lymphatic system disorders | | Leukopenia Eosinophilia | Thrombocytopenia Neutropenia | Bone marrow failure including aplastic anaemia, pancytopenia, agranulocytosis, haemolytic anaemia |
| Immune system disorders | | | Angioedema Hypersensitivity (see section 4.4) | Anaphylactic shock[1] Anaphylactoid shock[1] (see section 4.4) |

| | | | | |
|---|---|---|---|---|
| Endocrine disorders | | | Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) | |
| Metabolism and nutrition disorders | | Anorexia | Hypoglycaemia particularly in diabetic patients, Hypoglycaemic coma (see section 4.4) | Hyperglycaemia (see section 4.4) |
| Psychiatric disorders* | Insomnia | Anxiety Confusional state Nervousness | Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares, Delirium | Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt (see section 4.4) Mania |
| Nervous system disorders* | Headache Dizziness | Somnolence Tremor Dysgeusia | Convulsion (see sections 4.3 and 4.4) Paraesthesia, Memory impairment | Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension Myoclonus |
| Eye disorders* | | | Visual disturbances such as blurred vision (see section 4.4) | Transient vision loss (see section 4.4) uveitis |
| Ear and labyrinth | | Vertigo | Tinnitus | Hearing loss |

| | | | | |
|---|---|---|---|---|
| disorders* | | | | Hearing impaired |
| Cardiac disorders** | | | Tachycardia, Palpitation | Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged (see sections 4.4 and 4.9) |
| Vascular disorders** | Applies to iv form only: Phlebitis | | Hypotension | |
| Respiratory, thoracic and mediastinal disorders | | Dyspnoea | | Bronchospasm, Pneumonitis allergic |
| Gastrointestinal disorders | Diarrhoea Vomiting Nausea | Abdominal pain Dyspepsia Flatulence Constipation | | Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4) 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 (see section 4.4) Hepatitis |
| Skin and subcutaneous tissue disorders[2] | | Rash Pruritus Urticaria Hyperhidrosis | Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption | Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis Skin hyperpigmentation |

| | | | | |
|---|---|---|---|---|
| Musculoskeletal and connective tissue disorders* | | Arthralgia Myalgia | Tendon disorders including tendinitis, Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4) | Rhabdomyolysis Ligament rupture Muscle rupture Arthritis |
| Renal and Urinary disorders | | Blood creatinine increased | Renal failure acute (e.g. due to interstitial nephritis) | |
| General disorders and administration site conditions* | Applies to iv form only: Infusion site reaction (pain, reddening) | Asthenia | Pyrexia | Pain (including pain in back, chest, and extremities) |

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

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

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

• attacks of porphyria in patients with porphyria.

* 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, fatigue, psychiatric symptoms, memory impairment, 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

(see section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category).

** 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 (see section 4.4).

**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 gastrointestinal 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

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active substance ofloxacin.

*Mechanism of action*

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

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum ($C_{max}$) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

*Mechanism of resistance*

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 susceptible increased exposure organisms and susceptible increased exposure from resistant organisms are presented in the below table for MIC testing (mg/l).

EUCAST clinical MIC breakpoints for levofloxacin (version 10.0, 2020-01- 01):

| Pathogen | Susceptible | Resistant |
|---|---|---|
| Enterobacterales | ≤ 0.5 mg/l | >1 mg/l |
| *Pseudomonas* spp. | ≤ 0.001 mg/l | >1 mg/l |
| *Acinetobacter* spp. | ≤ 0.5 mg/l | >1 mg/l |

| | | |
|---|---|---|
| *Staphylococcus aureus* Coagulase-negative staphylococci | ≤ 0.001 mg/l | >1 mg/l |
| *Enterococcus spp.*[1] | ≤4 mg/l | >4 mg/l |
| *Streptococcus pneumoniae* | ≤ 0.001 mg/l | >2 mg/l |
| *Streptococcus* groups A,B,C and G | ≤ 0.001 mg/l | >2 mg/l |
| *Haemophilus influenzae* | ≤ 0.06 mg/l | >0.06 mg/l |
| *Moraxella catarrhalis* | ≤ 0.125 mg/l | >0.125 mg/l |
| *Helicobacter pylori* | ≤1 mg/l | >1 mg/l |
| *Aerococcus sanguinicola and urinae*[2] | ≤2 mg/l | >2 mg/l |
| *Aeromonas* spp. | ≤ 0.5 mg/l | >1 mg/l |
| PK/PD (Non-species related) breakpoints | ≤ 0.5 mg/l | >1 mg/l |
| 1: uncomplicated urinary tract infections only<br>2: Susceptibility can be inferred from ciprofloxacin susceptibility. | | |

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*

*Staphylococcus aureus methicillin-susceptible*

*Staphylococcus saprophyticus*

*Streptococci, group C and G*

*Streptococcus agalactiae*

*Streptococcus pneumoniae*

*Streptococcus pyogenes*

***Aerobic Gram-negative bacteria***

*Eikenella corrodens*

*Haemophilus influenzae*

*Haemophilus para-influenzae*

*Klebsiella oxytoca*

*Moraxella catarrhalis*

*Pasteurella multocida*

*Proteus vulgaris*

*Providencia rettgeri*

***Anaerobic bacteria***

*Peptostreptococcus*

***Other***

*Chlamydophila pneumoniae*

*Chlamydophila psittaci*

*Chlamydia trachomatis*

*Legionella pneumophila*

*Mycoplasma pneumoniae*

*Mycoplasma hominis*

*Ureaplasma urealyticum*

**Species for which acquired resistance may be a problem**

***Aerobic Gram-positive bacteria***

*Enterococcus faecalis*

*Staphylococcus aureus* methicillin-resistant*

Coagulase negative *Staphylococcus spp*

***Aerobic Gram-negative bacteria***

*Acinetobacter baumannii*

*Citrobacter freundii*

*Enterobacter aerogenes*
*Enterobacter cloacae*
*Escherichia coli*
*Klebsiella pneumoniae*
*Morganella morganii*
*Proteus mirabilis*
*Providencia stuartii*
*Pseudomonas aeruginosa*
*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 cerebrospinal 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 and are 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 (t½: 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 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| ClR [ml/min] | 13 | 26 | 57 |
| $t_{1/2}$ [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 after both oral and intravenous dosing showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay and it reduced tumour development in a photocarcinogenicity 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, Povidone BP, Purified water, Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate, Talc BP

### 6.2 Incompatibilities

Not applicable

### 6.3 Shelf life

36 Months

### 6.4 Special precautions for storage

Store below 30°C.

### 6.5 Nature and contents of container

Blister pack of 5 tablets

## 7. Marketing Authorization Holder

**MICRO LABS LIMITED**

31, Race Course Road

Bangalore 560001

INDIA

**Name and address manufacturing facility:**

**MICRO LABS LIMITED**

92, SIPCOT, Hosur-635 126, INDIA

## 8. Marketing Authorization Numbers

A4-5980

**9. Date of first authorization**

--

**10. Date of revision of the text**

March 2025