	ANFLOX Levofloxacin for Infusion 500mg/100ml
	MODULE 1

1. Name of the medicinal product

ANFLOX (Levofloxacin for Infusion 500mg/100ml)

2. Qualitative and quantitative composition

Batch Size: 1000 Litres **Shelf life:** 24 Months

Sr. No.	Ingredients	Specification	Qty./ ml	Qty. /1000 Litres.	Function
1	Levofloxacin Hemihydrate Eq. to Levofloxacin	IH	500 mg	50.0	Active
2	Sodium Chloride	BP	900 mg	90.0	Diluent
3	Water for injection	BP	Q.S.	Q.S	Vehicle

Where, BP: British Pharmacopoeia, IH: In- House Specification

3. Pharmaceutical form

Intravenous Infusion

4.1 Therapeutic indications

Levofloxacin 500 mg solution for infusion is indicated in adults for the treatment of the following infections.

• Community-acquired pneumonia

• Complicated skin and soft tissue infections

In complicated skin and soft tissue infections Levofloxacin 500 mg should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis and complicated urinary tract infections

• Chronic bacterial prostatitis

• Inhalation Anthrax: post exposure prophylaxis and curative treatment

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

4.2 Posology and method of administration

Posology

The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Treatment with Levofloxacin 500 mg after initial use of the intravenous preparation may be completed with an appropriate oral presentation according to the SPC of an appropriate oral presentation and as considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

The following dose recommendations can be given for Levofloxacin 500 mg:

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

Indication	**Daily dose regimen** (according to severity)	**Duration of treatment**[1] (according to severity)
Community-acquired pneumonia	500 mg once or twice daily	7-14 days
Pyelonephritis	500 mg once daily	7-10 days
Complicated urinary tract infections	500 mg once daily	7-14 days
Chronic bacterial prostatitis	500mg 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

[1]Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation but is normally 2 to 4 days

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 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 500 mg is contraindicated in children and growing adolescents.

Method of administration

Levofloxacin 500 mg solution for infusion is administered by slow intravenous infusion once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg Levofloxacin 500 mg solution for infusion

4.3 Contraindications

Levofloxacin 500 mg solution for infusion must not be used:

• in patients hypersensitive to levofloxacin or any other quinolone 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 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 (see also section 4.3).

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).

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.

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 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.

Infusion Time

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500mg Levofloxacin 500 mg solution for infusion should be observed. It is known, for ofloxacin, that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (l-isomer of ofloxacin) the infusion must be halted immediately.

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, 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) 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 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 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 500 mg 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.

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 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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

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

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

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

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoesthesia, 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

Hepatobiliary disorders

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

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing 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 test

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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin 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.

Important information about excipients

This medicinal product contains 177 mg sodium per 50 ml and 354 mg per 100 ml, equivalent to 8.85% and 17.7% respectively of the WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Levofloxacin 500 mg

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.

Effect of Levofloxacin 500 mg 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 anti-arrhythmics, 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.

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 . 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 500 mg must not be used in pregnant women.

Breast-feeding

Levofloxacin 500 mg 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

Fertility

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

4.7 Effects on ability to drive and use machines

Levofloxacin 500 mg has some undesirable effects (e.g. dizziness/vertigo, drowsiness, visual disturbances) which 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 are defined as follows:

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).

In the following table, adverse reactions are listed by system organ class and MedDRA-preferred term. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

MedDRA **System organ class**	**Frequency**	**Undesirable Effects**
Infections and infestations	Uncommon	Fungal infection including Candida infection, Pathogen resistance
Blood and lymphatic system disorders	Uncommon	Leukopenia, Eosinophilia
	Rare	Thrombocytopenia, Neutropenia
	Not known	Pancytopenia, Agranulocytosis, Haemolytic anaemia
Immune system disorders	Rare	Angioedema, Hypersensitivity
	Not known	Anaphylactic shock[a], Anaphylactoid shock[a] ,
Metabolism and	Uncommon	Anorexia

nutritional disorders	Rare	Hypoglycaemia particularly in diabetic patients
	Not known	Hyperglycaemia, Hypoglycaemic coma
Psychiatric disorders*	Common	Insomnia
	Uncommon	Anxiety, Confusional state, Nervousness
	Rare	Psychotic reactions (with e.g. hallucination, paranoia), Depression, Agitation, Abnormal dreams, Nightmares
	Not known	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt
Nervous system disorders*	Common	Headache, Dizziness
	Uncommon	Somnolence, Tremor, Dysgeusia
	Rare	Convulsion, Paraesthesia
	Not known	Peripheral sensory neuropathy, Peripheral sensory motor neuropathy, Parosmia including anosmia, Dyskinesia, Extrapyramidal disorder, Ageusia, Syncope, Benign intracranial hypertension
Eye disorders*	Rare	Visual disturbances such as blurred vision
	Not known	Transient vision loss
Ear and Labyrinth disorders*	Uncommon	Vertigo
	Rare	Tinnitus
	Not known	Hearing loss, Hearing impaired
Cardiac disorders**	Rare	Tachycardia, Palpitation
	Not known	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

Vascular disorders**	Common	Phlebitis
	Rare	Hypotension
Respiratory, thoracic and mediastinal disorders	Uncommon	Dyspnoea
	Not known	Bronchospasm, Pneumonitis allergic
Gastrointestinal disorders	Common	Diarrhoea, Vomiting, Nausea
	Uncommon	Abdominal pain, Dyspepsia, Flatulence, Constipation
	Not known	Diarrhoea–haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, Pancreatitis
Hepatobiliary disorders	Common	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
	Uncommon	Blood bilirubin increased
	Not known	Jaundice and severe liver injury, including fatal cases with acute liver failure, primarily in patients with severe underlying diseases, Hepatitis
Skin and subcutaneous tissue disorders[b]	Uncommon	Rash, Pruritus, Urticaria, Hyperhidrosis
	Not known	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction, Leukocytoclastic vasculitis, Stomatitis
	Rare	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption
Musculo-skeletal and connective tissue disorders*	Uncommon	Arthralgia, Myalgia
	Rare	Tendon disorder, including tendinitis (e.g. Achilles tendon), Muscular weakness which may be of special importance in patients with myasthenia gravis
	Not known	Rhabdomyolysis, Tendon rupture (e.g. Achilles tendon), Ligament rupture, Muscle rupture,

		Arthritis
Renal and urinary disorders	Uncommon	Blood creatinine increased
	Rare	Renal failure acute (e.g. due to interstitial nephritis)
General disorders and administration site conditions*	Common	Infusion site reaction (pain, reddening)
	Uncommon	Asthenia
	Rare	Pyrexia
	Not known	Pain (including pain in back, chest, and extremities)
Endocrine disorders	Rare	Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

[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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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 500 mg solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.

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

Management

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. 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-DNA-gyrase complex and topoisomerase IV.

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 intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriaceae	≤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]	≤1 mg/L	>1 mg/L
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

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 intra 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 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.

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).

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
Sodium chloride
Water for injection

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage
Store in a dry place at a temperature below 30°C.

6.5 Nature and contents of container

A clear yellowish colour solution 100 ml PE bottle in carton along with insert.

6.6 Special precautions for disposal and other handling

Not applicable.

7. Marketing Authorization
Holder
PROMED PHARMACEUTICALS LTD
P.O Box 22953-00100
Nairobi, Kenya.

Manufacturer
REALCADE LIFESCIENCE PVT. LTD.
Survey No, 891-892, Y-Junction,
At Narmada Canal Karannagar,
Ta: Kadi, 382715 Mehsana Gujrat, India.

8. Marketing authorization number(s)
Not applicable.

9. Date of first authorization/renewal of the authorization
Not applicable.

10. Date of revision of the text