

1.3 Product Information

1.3.1 Summary of product characteristics (SmPC)

1. **Name of the medicinal product: LEVOFLOXACIN 500 MG TABLET**
(Levofloxacin Tablets USP 500 mg)

2. **Qualitative and quantitative composition:**

Each film coated tablet contains:

Levofloxacin Hemihydrate USP Equivalent to Levofloxacin (500 mg)

Approved Colour Used. (-)

Excipients (QS)

Sr. No.	Ingredients	Specification	Label Claim / Tablet (In mg)	Over ages added (In %)	Qty. / Tablet (In mg)	Reason for Function
a) Dry Mixing						
1.	Levofloxacin Hemihydrate	USP	Levofloxacin Hemihydrate equivalent to Levofloxacin (anhydrous) 500.00 mg)	NA	514.00	Medicament
2.	Lactose monohydrate	BP	NA	NA	59.79	Diluent
3.	Maize starch	BP	NA	NA	34.49	Diluent
b) Binder Preparation						
4.	Maize starch	BP	NA	NA	28.41	Binder
5.	Povidone (K 30)	BP	NA	NA	5.00	Binder
6.	Methyl hydroxybenzoate	BP	NA	NA	0.38	Preservative
7.	Propyl hydroxybenzoate	BP	NA	NA	0.09	Preservative
8.	Purified water	BP	NA	NA	-----	Vehicle
c) Lubrication						
9.	Purified talc	BP	NA	NA	7.95	Glidant
10.	Magnesium stearate	BP	NA	NA	5.00	Lubricant
11.	Croscarmellose sodium	BP	NA	NA	19.89	Disintegrant
12.	Colloidal anhydrous silica	BP	NA	NA	5.00	Glidant
Average Weight of Uncoated Tablet (In mg)					680.00	
d) Coating						
13.	Hypromellose (15 CPS)	BP	NA	NA	9.00	Film-Former
14.	Titanium dioxide	BP	NA	NA	1.50	Opacifier
15.	Purified talc	BP	NA	NA	4.00	Antiadherent
16.	Macrogol 6000	BP	NA	NA	0.90	Plasticizer
17.	Sunset yellow lake	In-House	NA	NA	0.60	Colour
18.	Purified water	BP	NA	NA	-----	Vehicle
Average Weight of Film Coated Tablet (In mg)					696.00	

3 Pharmaceutical form: Film coated Tablet

Description: Orange coloured, capsule shaped, biconvex, film coated tablet, breakline on one side, plain on other side.

4 Clinical Particulars

1.3.1.4.1 Therapeutic indications:

LEVOFLOXACIN 500 MG (Levofloxacin Tablets USP 500 mg) are indicated for the treatment of Acute bacterial sinusitis, Acute exacerbations of chronic bronchitis, Community- acquired pneumonia, Complicated skin and soft tissue infections, Pyelonephritis and complicated urinary tract infections, Chronic bacterial prostatitis, Uncomplicated cystitis, Inhalation Anthrax: post exposure prophylaxis and curative treatment.

1.3.1.4.2 Posology and method of administration

Route: Oral

Method of Administration:

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

Treatment time

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

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 (<i>according to severity</i>)
Acute bacterial sinusitis	500 mg once daily	10 - 14 days
Acute exacerbations of chronic obstructive pulmonary disease including bronchitis	500 mg once daily	7 - 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Acute pyelonephritis	500 mg once daily	7 - 10 days
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Uncomplicated cystitis	250 mg once daily	3 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500 mg once or twice daily	7 - 14 days

Inhalation Anthrax	500 mg once daily	8 weeks
--------------------	-------------------	---------

Special Populations

Impaired renal function (creatinine clearance $\leq$ 50 ml/min)

Creatinine clearance	Dosage regimen		
	250 mg/24 h	500 mg/24 h	500 mg/12 h
	First dose: 250 mg	First dose: 500 mg	First dose: 500 mg
50-20 ml/min	Then: 125 mg/24h	Then: 250 mg/24 h	Then: 250 mg/12 h
19-10 ml/min	Then: 125 mg/48 h	Then: 125 mg/24 h	Then: 125 mg/12 h
< 10 ml/min (including haemodialysis and CAPD) ¹	Then: 125 mg/48 h	Then: 125 mg/24 h	Then: 125 mg/24 h

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

Impaired liver function

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

Elderly population

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

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents.

1.3.1.4.3 Contraindications

LEVOFLOXACIN 500 MG (Levofloxacin Tablets USP 500 mg) must not be used:

- In patients hypersensitive to levofloxacin or other quinolones or any of the excipients.
- 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.

1.3.1.4.4 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.

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

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 in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

Methicillin-resistant Staphylococcus aureus (MRSA)

Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

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

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

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

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. The daily dose should be adjusted in elderly patients based on creatinine clearance.

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

Clostridium difficile-associated disease

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

Patients predisposed to seizures

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

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

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

Hypersensitivity reactions

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

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin. At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia

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

Prevention of photosensitisation

Photosensitisation has been reported with levofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

QT interval prolongation

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

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

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

Peripheral neuropathy

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.

Hepatobiliary disorders

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

Exacerbation of myasthenia gravis

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

Vision disorders

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

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.

1.3.1.4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin

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

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with Levofloxacin Tablets. Concurrent administration of fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts or magnesium- or aluminium-containing antacids, or didanosine (*only didanosine formulations with aluminium or magnesium containing buffering*

agents) should not be taken 2 hours before or after Levofloxacin Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

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

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

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13 % higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

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

Caution should be exercised when levofloxacin is coadministered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

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

- calcium carbonate
- digoxin
- glibenclamide
- ranitidine.

Effect of levofloxacin on other medicinal products

Ciclosporin

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

Vitamin K antagonists

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

Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.

Drugs known to prolong the QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic).

Other relevant information

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

Other forms of interactions

Meals

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

1.3.1.4.6 Pregnancy and Lactation

Pregnancy

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

Lactation

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

1.3.1.4.7 Effects 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).

1.3.1.4.8 Undesirable effects

The most common side effects are

- Hypersensitivity Reactions
- Hepatotoxicity
- Peripheral Neuropathy
- Central Nervous System Effects
- Exacerbation of Myasthenia Gravis

The most common side effects in children are: fever, cough, vomiting, headache, loss of appetite.

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

Frequencies are defined using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

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

System organ class	Common ($\geq 1/100$ to <1/10)	Uncommon ($\geq 1/1,000$ to <1/100)	Rare ($\geq 1/10,000$ 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	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity	Anaphylactic shock ^a Anaphylactoid shock ^a

Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders*	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt
Nervous system disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion Paraesthesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension
Eye disorders*			Visual disturbances such as blurred vision	Transient vision loss
Ear and Labyrinth disorders*		Vertigo	Tinnitus	Hearing loss 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.
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting	Abdominal pain Dyspepsia		Diarrhoea – haemorrhagic which in

	Nausea	Flatulence Constipation		very rare cases may be indicative of enterocolitis, including pseudomembranous colitis 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 Hepatitis
Skin and subcutaneous tissue disorders ^b		Rash Pruritus Urticaria Hyperhidrosis	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction Leukocytoclastic vasculitis Stomatitis
Endocrine disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) 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*		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

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

^b Mucocutaneous reactions may sometimes occur even after the first dose

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses

(including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

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

- attacks of porphyria in patients with porphyria.

1.3.1.4.9 Overdoses

Symptoms:

Overdose includes liver damage, a dry mouth, large pupils, flushing, nausea, vomiting, abdominal pain, diarrhea, seizures, sweating, haemodynamic changes and cardiovascular collapse with respiratory depression. If above symptoms observed, seek emergency medical attention.

Treatment:

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

1.3.1.5.1 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 drug substance ofloxacin.

Mechanism of action

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

PK/PD relationship

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

Mechanism(s) of 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.

1.3.1.5.2 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 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 ($t_{1/2}$: 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 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.

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

1.3.1.5.3 Preclinical safety Data:

Not Applicable

6 Pharmaceutical particulars

1.3.1.6.1 List of excipients

Lactose Monohydrate, Maize Starch, Povidone K-30, Methyl Hydroxybenzoate, Propyl Hydroxybenzoate, Purified Water, Purified Talc, Magnesium Stearate, Croscarmellose sodium, Colloidal Anhydrous Silica, Hypromellose, Titanium Dioxide, Macrogol-6000, Sunset Yellow Lake.

1.3.1.6.2 Incompatibilities

Not applicable

1.3.1.6.3 Shelf life

36 months

1.3.1.6.4 Special precautions for storage

Store below 30°C in a dry & dark place.

Keep all medicines out of reach of children.

1.3.1.6.5 Nature and contents of container

Primary packing: 10 Tablets in an ALU-ALU Blister

Secondary packing: 10 Blisters are packed in a carton along with leaflet.

Tertiary packing: Such 10 cartons are packed in a shrink. Such 20 Shrinks are packed in a 5 Ply shipper sealed with BOPP tape & strap with strapping roll.

1.3.1.6.5 Special precautions for disposal and other handling

None.

7 Applicant / Manufacturer

Applicant

Applicant name and address	M/s. AREPHARM AND AGROVET LTD. No 46/47 Haco House, Igbo Road, Kano
Contact person's phone number	
Contact person's email	

Manufacturer

Manufacturer name and address	M/s. IMPULSE PHARMA PVT. LTD. J-201, J-202/1 , MIDC Tarapur, Boisar, Dist. Palghar - 401506, Maharashtra State, India.
Contact person's phone number	+91 7350864803
Contact person's email	pravin.patil@kamlagroup.co.in