1.6 Product Information

1.6.1 Prescribing Information (Summary of Product Characteristics)

1. Name of the Medicinal Product

1.1 Trade Name : LEVOC 500 (Levofloxacin Tablets USP 500 mg)

1.2 Strength : 500 mg

1.3 Pharmaceutical Form : Film Coated Tablets

2. Qualitative and Quantitative Composition

S. No	Name of Ingredients	Quantity/ Tablets (mg)
Active Substance		
1	Levofloxacin Hemihydrate eq. to Levofloxacin*	512.47 ≈ 500.00
Inactive Substance		
2	Maize Starch	79.53
3	Croscarmellose Sodium	48.00
4	Microcrystalline Cellulose	33.00
5	Purified Talc	22.00
6	Colloidal Anhydrous Silica	20.00
7	Sodium Starch Glycolate (Type A)	20.00
8	Magnesium Stearate	10.00
9	Opadry Yellow	10.00
10	Purified Water**	Q.S.
	Total	**755.00 mg**

Remark:

*Molecular weight of Levofloxacin Hemihydrate = 370.38

Molecular weight of Levofloxacin = 361.37

Therefore, 512.47 mg Levofloxacin Hemihydrate ≈ 500.00 mg Levofloxacin

** Gets evaporated during manufacturing process and does not remain in the final product.

3. Pharmaceutical Form

'Film coated Tablet

Light yellow color, caplet shaped, film coated tablets having break line on one side and plain on other side.

4. Clinical Particulars

4.1 Therapeutic indications

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

• Acute bacterial sinusitis
• Acute exacerbations of chronic bronchitis
• Community-acquired pneumonia
• Complicated skin and soft tissue infections

For the above-mentioned infections Levofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

• Pyelonephritis and complicated urinary tract infections
• Chronic bacterial prostatitis
• Uncomplicated cystitis
• Inhalation Anthrax: postexposure prophylaxis and curative treatment

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

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

4.2 Posology and method of administration

Levofloxacin dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.

Levofloxacin 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:

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 bronchitis	500 mg once daily	7 - 10 days

Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Pyelonephritis	500 mg once daily	7 – 10 days
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

Renal impairment (creatinine clearance ≤50 ml/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)	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/24 h

Hepatic impairment: 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: No adjustment of dose is required in the elderly, other than that imposed by consideration of renal function.

Paediatric population: Levofloxacin is contraindicated in children and growing adolescents.

Method of administration

Oral administration

Levofloxacin tablets should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals. Levofloxacin should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents), and sucralfate administration, since reduction of absorption can occur.

4.3 Contraindication

Levofloxacin contraindicated in following:

- In patients hypersensitive to the active substance or other quinolones or to 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.

4.4 Special warnings and special precautions for use

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).

Tendinitis and tendon rupture: Close monitoring of elderly patients is necessary if they are prescribed levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon

Clostridium difficile-associated disease (CDAC): 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: Levofloxacin is contraindicated in patients with a history of epilepsy. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency: 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 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 bullous reactions: Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

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 photosensitization: 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: Coagulation tests should be monitored when these drugs are given concomitantly with Levofloxacin.
Psychotic reactions: 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. 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.
Peripheral neuropathy: Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.
Hepatobiliary disorders: 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: 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: If superinfection occurs during therapy, appropriate measures should be taken.

4.5 Interaction with other medicinal products and other forms of interaction
Iron salts, zinc salts, magnesium- or aluminium-containing antacids and 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. Hence these drug should not be taken 2 hours before or after levofloxacin administration.
Sucralfate: The bioavailability of levofloxacin is significantly reduced when administered together with sucralfate. It is best to administer sucralfate 2 hours after the levofloxacin administration.
Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs: No pharmacokinetic interactions of levofloxacin with theophylline, 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: Caution should be exercised when levofloxacin is co-administered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.
Ciclosporin: The half-life of ciclosporin was increased by 33% when co-administered with levofloxacin.
Vitamin K antagonists: Coagulation tests, should be monitored in patients treated with vitamin K antagonists.
Drugs known to prolong QT interval: Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics.

4.6 Pregnancy and lactation
Pregnancy: Levofloxacin must not be used in pregnant women.
Breast-feeding: Levofloxacin is contraindicated in breast-feeding women

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

4.8 Undesirable effects
The most commonly reported adverse reaction is dizziness. Serious angioedema may occur rarely (≥1/10,000 to <1/1,000). The reactions are classified according to frequency very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known.
Common: Insomnia, Headache, Dizziness, Diarrhoea, Vomiting, Nausea, Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT),
Uncommon: Fungal infection including Candida infection, Pathogen resistance, Eosinophilia, Leukopenia, Anorexia, Confusional state, Anxiety, Nervousness, Somnolence, Tremor, Dysgeusia, Vertigo, Dyspnoea, Abdominal pain, Dyspepsia, Flatulence, Constipation, Blood bilirubin increased, Rash, Pruritus, Urticaria, Hyperhidrosis, Arthralgia, Myalgia, Blood creatinine increased, Asthenia.
Rare: Neutropenia, Thrombocytopenia, Angioedema, Hypersensitivity, Hypoglycaemia, particularly in diabetic patients, Psychotic reactions (with e.g. hallucination, paranoia), Depression, Agitation, Abnormal dreams, Nightmares, Convulsion, Paraesthesia, Visual disturbances such as blurred vision, Tinnitus, Tachycardia, Palpitation, Hypotension, Tendon disorder including tendinitis (e.g. Achilles tendon), Muscular weakness which may be of special importance in patients with myasthenia gravis, Renal failure acute (e.g. due to interstitial nephritis), Pyrexia

Not Known: Haemolytic anaemia, Pancytopenia, Agranulocytosis, Anaphylactic shock, Anaphylactoid shock, Hyperglycaemia, Hypoglycaemic coma, Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt, Peripheral sensory neuropathy, Peripheral sensory motor neuropathy, Parosmia including anosmia, Dyskinesia, Extrapyramidal disorder, Ageusia, Syncope, Benign intracranial hypertension, Transient vision loss), uveitis, Hearing loss, Hearing impaired, Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), Electrocardiogram QT prolonged, Bronchospasm, Pneumonitis, allergic, Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, Pancreatitis, Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases, Hepatitis, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction, Leukocytoclastic vasculitis, Stomatitis, Rhabdomyolysis, Tendon rupture (e.g. Achilles tendon), Ligament rupture, Muscle rupture, Arthritis, Pain (including pain in back, chest, and extremities)

4.9 Overdose

Symptoms: Central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.

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

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : quinolone antibacterials, fluoroquinolones.

ATC code : J01 MA12

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.

PK/PD relationship: The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum Cmax or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

Mechanism of resistance: Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

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 approximately 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.

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 (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.

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.

6 Pharmaceutical Particulars

6.1 List of excipients

Maize Starch
Croscarmellose sodium
Microcrystalline Cellulose
Purified Talc
Colloidal anhydrous silica
Sodium starch glycolate (Type A)
Magnesium stearate
Opadry yellow

6.2 Incompatibilities

None

6.3 Shelf life
3 years from the date of manufacture

6.4 Special precautions for storage
Store at temperature not exceeding 30°C, protect from light and moisture.

6.5 Nature and contents of container
3 x 10 Film coated tablets in Alu-Alu Blister Pack.

6.6 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Authorization Holder
ZIM Laboratories Limited
B-21/22, MIDC Area,
Kalmeshwar, Nagpur 441501
Maharashtra State,
India.

8. Number(S) In the National Register of Finished pharmaceutical products
NA

9. Date of First Authorization/Renewal of the Authorization
NA

10. Date of Revision of the Text
01 July 2019