LEVOXIN should be administered at least two hours before or two hours after antacids containing magnesium or aluminum, sucralfate, metal cations such as iron, and multivitamin preparations with zinc or didanosine chewable tablets.

Dosage in patients with renal impairment:

Following dose diagram is used for the patients having creatinine clearance lower than 80 ml/min. If only serum creatinine concentration is known, creatinine clearance can be calculated according to the following formula:

For male:

Creatinine clearance (ml/min) = Weight (kg) x (140-age) / 72 x serum creatinine (mg/dL)

For female: 0.85 x value calculated for male

Creatinine value used in this calculation should represent a proper working (steady-state) kidney.

Dosage in patients with renal impairment:

Status of Kidney	Starting Dose	Following Doses
Acute bacterial exacerbation of chronic bronchitis / Community-acquired pneumonia / Acute maxillary sinusitis / Skin and subcutaneous tissue infections without complication / Chronic bacterial prostatitis		
Cl_{CR} 50-80 ml/min	No dosage adjustment is required	No dosage adjustment is required
Cl_{CR} 20-49 ml/min	500 mg	250 mg / 24 hr
Cl_{CR} 10-19 ml/min	500 mg	250 mg / 48 hr
Hemodialysis	500 mg	250 mg / 48 hr
Chronic ambulatory peritoneal dialysis	500 mg	250 mg / 48 hr
Complicated skin and subcutaneous tissue infections / Nosocomial pneumonia		
Cl_{CR} 50-80 ml/min	No dosage adjustment is required	No dosage adjustment is required
Cl_{CR} 20-49 ml/min	750 mg	750 mg / 24 hr
Cl_{CR} 10-19 ml/min	750 mg	500 mg / 48 hr
Hemodialysis	750 mg	500 mg / 48 hr
Chronic ambulatory peritoneal dialysis	750 mg	500 mg / 48 hr
Complicated urinary tract infections / Acute pyelonephritis		
CLCR ≥ 20 ml/min	No dosage adjustment is required	No dosage adjustment is required
Cl_{CR} 10-19 ml/min	250 mg	25 mg / 48 hr
Uncomplicated urinary tract infections	No dosage adjustment is required	

Cl_{CR} = Creatinine clearance

OVERDOSE and PRECAUTIONS:

Levofloxacin exhibits a low potential for acute toxicity. In the event of an overdosage, the stomach should be emptied, the patient should be observed and appropriate hydration should be maintained, symptomatic and adjuvant therapy should be performed. Any antidote against levofloxacin is not known. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis.

STORAGE CONDITIONS:

Store at room temperature below 25°C in the original package. Keep out of the reach of children.

TRADE DRESS and PACKAGING CONTENT:

LEVOXIN 500 mg Film Coated Tablet, in blister packs containing 7 film coated tablets

PRODUCT LICENCE HOLDER:

The holder of trade mark and marketing authorization holder

BioActiveT United Kingdom

By prescription only.

BioActiveT United Kingdom

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LEVOXIN 500 mg FILM COATED TABLET

FORMULA :Each film coated tablet contains;
Levofloxacin hemihydrate equivalent to 500 mg levofloxacin.
Titanium dioxide, yellow iron oxide and red iron oxide are used as coloring agents.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties:

Levofloxacin is the L-isomer of the racemate, ofloxacin, a quinolone antimicrobial agent. The antibacterial activity of ofloxacin resides primarily in the L-isomer. The mechanism of action of levofloxacin involves inhibition of bacterial topoisomerase IV and DNA gyrase enzymes.

These both which are type II topoisomerases are required for DNA replication, transcription, repair and recombination in bacteria. Bactericide concentrations of Levofloxacin are equal to or slightly greater than bacteriostatic concentrations. Since levofloxacin differ in chemical structure and mode of action, it is mostly active against bacteria resistant to β-lactam antibiotics. Resistance to levofloxacin due to spontaneous mutation in vitro is a rare occurrence, with 10^{-9} to 10^{-10} frequency. Levofloxacin has a wide range of activity spectrum and is active against most of gram-negative and gram-positive microorganisms. Levofloxacin has been shown to be active against the following microorganisms both in vitro and in clinical infections:

Aerobic gram-positive microorganisms: *Enterococcus faecalis* (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains), *Staphylococcus epidermidis* (methicillin-susceptible strains) *Staphylococcus saprophyticus, Streptococcus pneumoniae* (including penicillin-susceptible strains*) *Streptococcus pyogenes.*

* Note: For penicillin- resistant *S.pneumoniae* strains, penicillin MIC value is ≥ 2 mcg/ml

Aerobic gram-negative microorganisms: *Enterobacter cloacae, Escherichia coli, Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, Pseudomonas aeruginosa, Serratia marcescens.*

As with other drugs in quinolone group, some strains of Pseudomonas aeruginosa develop resistance fairly rapidly against Levofloxacin.

Other Microorganisms: *Chlamydia pneumoniae, Mycoplasma pneumoniae.*

The clinical significance of the following in vitro data is unknown. Levofloxacin exhibits minimum inhibitory concentrations (MIC values) of below 2 mcg/ml against most (90%) strains of the following microorganisms.

However, the safety and effectiveness of Levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus haemolyticus, Streptococcus (Group C/F), *Streptococcus* (Group G), *Streptococcus agalactiae, Streptococcus milleri*, Viridans group streptococci

Aerobic gram-negative microorganisms

Acinetobacter baumannii, Acinetobacter lwoffii, Bordatella pertussis, Citrobacter (diversus) *koseri, Citrobacter freundii, Enterobacter aerogenes, Enterobacter sakazakii, Klebsiella oxytoca, Morganella morganii, Pantoea* (Enterobacter) *agglomerans, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas fluorescens*

Anaerobic gram-positive microorganisms

Clostridium perfringens

Pharmacokinetic Properties:

Absorption: Levofloxacin is rapidly and essentially completely absorbed after oral administration. The absolute bioavailability of levofloxacin from a 500 mg oral dose is approximately 99%. Peak plasma concentrations are obtained 1-2 hr. Levofloxacin pharmacokinetics are linear and predictable after single and multiple dosing regimens. Steady-state conditions are reached within 48 hours following a 500 mg once-daily dosage regimen. Following repeated once-daily dosage regimens, upper and lower limits of plasma are 5.7 (±1.4) and 0.5 (±0.2) mcg/ml, respectively at steady state. Administration of Levofloxacin without regard to food does not affect clinical pharmacokinetics significantly.

Distribution: The mean volume of distribution of levofloxacin ranges from 74 to 112 L after single and multiple 500 mg dosing. Concentration in blister fluid is in the same level with respect to plasma concentrations, whereas dermal tissue concentrations are 2 and lung tissue concentrations are 2 to 5 fold higher than plasma concentrations. Levofloxacin is approximately 24 to 38% bound to plasma proteins (mainly to albumin).

Metabolism: Levofloxacin is stereochemically stable in plasma and urine and does not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin is metabolized to a very small extent and most of it (87%) is recovered as uncharged drug in urine within 48 hours, whereas a small portion (4%) of the dose is recovered in feces in 72 hours. Less than 5% of an administered dose is recovered in the urine as the desmethyl and N-oxide metabolites. These metabolites have no pharmacological activity.

Excretion: The mean terminal plasma elimination half-life of levofloxacin ranges from 6 to 8 hours, total body clearance of levofloxacin ranges from 144 to 226 ml/min and renal clearance of levofloxacin ranges from 96 to 142 ml/min. Administration of either cimetidine or probenecid results in approximately 24% and 35% reduction in the levofloxacin renal clearance, respectively. No levofloxacin crystals were found in any of the urine samples freshly collected from subjects receiving Levofloxacin.

Special patient groups: There are no clinically significant differences in levofloxacin pharmacokinetics in terms of age, sex and race. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin is not expected to be affected by hepatic impairment.

Renal Impairment: Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance ≤ 50 ml/min). Dosage adjustment is required in such patients to avoid accumulation.

Neither hemodialysis nor continuous ambulatory peritoneal dialysis is effective in removal of levofloxacin from the body. Because of this, supplemental doses of levofloxacin are not required following hemodialysis.

INDICATIONS:

LEVOXIN is indicated for the treatment of adults (≥ 18 years of age) with mild, moderate, and severe infections caused by susceptible bacteria as listed below:

Acute maxillary sinusitis: Due to *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis.*

Acute bacterial exacerbation of chronic bronchitis: Due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae or Moraxella catarrhalis.*

Nosocomial Pneumonia: Due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae, or Streptococcus pneumoniae.*

Adjunctive therapy is used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

Community-acquired pneumonia: Due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains, MIC value for penicillin is > 2 mcg/ml), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila or Mycoplasma pneumoniae.*

Complicated skin and skin structure infections: Due to methicillin susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes or Proteus mirabilis*

Uncomplicated skin and skin structure infections: Mild to moderate abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*.
Chronic bacterial prostatitis: Due to *Escherichia coli, Enterococcus faecalis* or *Staphylococcus aureus*.
Complicated urinary track infections: (mild or moderate) due to *Enterococcus faecalis, Enterobacter cloacea, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Pseudomonas aeruginosa*.
Acute pyelonephritis: (mild or moderate) due to *Escherichia coli*.
Uncomplicated urinary track infections: (mild or moderate) due to *Escherichia coli, Klebsiella pneumoniae* or *Staphylococcus saprophyticus*.
Appropriate culture and susceptibility tests should be performed before the treatment in order to isolate and identify organisms causing the infection and to determine their susceptibility to levofloxacin. Therapy with levofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be selected.
As with other antibiotics, some strains of Pseudomonas aeruginosa may develop resistance fairly rapidly during treatment with levofloxacin. Due to this, susceptibility testing should be performed periodically during therapy.

CONTRAINDICATIONS:
LEVOXIN is contraindicated in persons with known hypersensitivity to levofloxacin, or other quinolone antibiotics or any other ingredient in the drug.

WARNINGS / PRECAUTIONS:
WARNINGS
The safety and efficacy of levofloxacin in adolescents (< 18 years of age), pregnant women and nursing mothers have not been determined. In immature rats and dogs, administration of levofloxacin resulted in increased frequency and severity of osteochondrosis. Other quinolones also produce erosions in the weight-bearing joints and arthropathy in animals of various species. Convulsions and toxic psychosis have been reported in patients taking quinolone compounds, including Levofloxacin. Quinolones may also lead to intracranial pressure increase and central nervous system (CNS) stimulation. In those cases, drug therapy should be discontinued and appropriate therapy should be performed. LEVOXIN should be used with caution in patients with central nervous system (CNS) disorder lowering the convulsion threshold.

- *Acute hypersensitivity reactions* may be seen during the therapy with quinolones including anaphylactics. LEVOXIN therapy should be discontinued at the first sign of allergy.
- Serious anaphylactic reactions may require treatment with epinephrine, oxygen, intravenous fluids, antihistamines, corticosteroids, vasopressor amines and intubation.
- *Clostridium difficile*-associated pseudomembranous colitis may happen with use of all antibiotics. In such a case, LEVOXIN should be discontinued and an appropriate therapy should be started. In mild cases, discontinuation of drug is sufficient. Water and electrolytes, protein supplementation and antibiotic treatment of *Clostridium difficile* may be needed in further severe cases.

Shoulder, hand and tendon ruptures have been reported in patients taking quinolones including levofloxacin. This risk is further increased in older patients in those taking corticosteroid drugs.

- LEVOXIN should be discontinued if the patient experiences pain, inflammation or rupture of a tendon and the patient should avoid movement until the diagnosis of not having rupture.

WARNINGS
General
- Although solubility of levofloxacin is higher than other quinolones, patients should drink water liberally while taking LEVOXIN to avoid formation of highly concentrated urine.
- LEVOXIN should be used with caution in patients with impaired renal function (creatinine clearance < 50 ml/min). Dosage adjustment may be required.
- Phototoxic reactions can be seen during therapy with quinolones. Patients should be warned against excessive exposure to daylight and levofloxacin therapy should be discontinued when first photosensitivity symptom occurs.
- Levofloxacin should be used with caution in central nervous system (CNS) disorders lowering the convulsion threshold.
- Glucose levels in plasma should be monitored closely in patients being treated with insulin or an oral antidiabetic. If a hypoglycemic reaction occurs, levofloxacin therapy should be discontinued and an appropriate therapy should be started.

- Some quinolones, including levofloxacin, have been associated with prolongation of the QT interval and infrequent cases of arrhythmia on the electrocardiogram. Rare cases of torsade de pointes have been reported. Drugs that prolong QT interval to minimize the arrhythmia risk, Class IA and Class III antiarrhythmic agents should be avoided and LEVOXIN should not be used if there are hypokalemia, severe bradycardia or cardiomyopathy that create the risk factor for torsades de pointes.

Use in Pregnancy and Lactation:
Use in pregnancy: Pregnancy Category C
There are no adequate and well-controlled studies in pregnant women to investigate the effect of Levofloxacin on pregnancy. LEVOXIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Use in lactation: Levofloxacin determination in human milk has not been performed. However, possibility of excretion into human milk is high. Nursing mothers should discontinue either nursing or levofloxacin therapy.
Pediatric patients: The safety and efficacy of levofloxacin in children and adolescents under 18 years of age has not been investigated.
Geriatric patients: The safety, efficacy and pharmacokinetic properties of levofloxacin in younger adults and elderly adults do not differ significantly. However, elderly patients are more likely to have decreased renal function; care should be taken in dose selection.
Ability to drive and use machines: Levofloxacin may cause neurologic adverse effects (dizziness, lightheadedness) in some patients. Patients should be provided with how the drug affects them before they drive and use machines.

ADVERSE REACTIONS:
Frequency of adverse reactions reported in clinical studies is 6.3%. 4% of the patients treated with levofloxacin have discontinued the therapy due to adverse reactions.
It is considered that following adverse reactions are due to levofloxacin therapy:
Nausea 1.3%, diarrhea 1%, vaginitis 0.8%, insomnia 0.4%, abdominal pain 0.5%, flatulence 0.3%, pruritus 0.3%, lightheadedness 0.3%, dyspepsia 0.3%, skin rash 0.3%, genital moniliasis 0.2%, taste disturbance 0.2%, emesis 0.2%, constipation 0.1%, fungal infection 0.1%, genital pruritus 0.1%, headache 0.1%, moniliasis 0.1%, nervousness 0.1%, erythematous rash 0.1%, urticaria 0.1%, maculopapular rash 0.1%.
In clinical studies following adverse reactions have been reported over a 3% frequency. Relevance with levofloxacin has not been considered.
Nausea 7%, headache 6.1%, diarrhea 5.7%, insomnia 4.2%, constipation 3.3%
Without considering the relevance with drug, following adverse reactions have been reported with a frequency between 1% and 3%:

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Lightheadedness 2.5%, abdominal pain, dyspepsia 2.3%, emisis 2.3%, vaginitis 1.8%, flatulence 1.4%, pain 1.4%, pruritus 1.3%, sinusitis 1.3%, chest pain 1.1%, fatigue 1.3%, skin rash 1.4%, back pain 1.1%, rhinitis 1.1%, dyspnea 1.1%, pharyngitis 1%.
With treatments of other quinolones, cataract and lens opacities have been reported. The relation between these reactions and taken drugs are unknown.

Crystalluria and cylindruria have been reported with other quinolones.
Following anomalies in laboratory values has been reported more than 2% of patients.
It is uncertain whether it is associated with the drug or the treated disease.
Blood biochemistry: Decrease in glucose (2.2%)
Hematology: Decrease in lymphocyte (2.3%)
Post-marketing adverse reactions:
Allergic pneumonia, anaphylactic shock, anaphylactic reaction, dysphonia, abnormal EEG, encephalopathy, eosinophile, erythema multiforme, hemolytic anemia, multi-system organ failure, elevations of the prothrombin time (International Normalized Ratio-INR), Stevens-Johnson syndrome, tendon rupture, torsades de pointes, vasodilation.

IN THE EVENT OF AN UNEXPECTED REACTION CONSULT YOUR PHYSICIAN.

DRUG INTERACTIONS:
Antacids, Sucralfate, Metal Cations, Multivitamins
Antacids containing magnesium, or aluminum, sucralfate, metal cations such as iron, and multivitamin preparations with zinc and didanosine may interfere with the absorption of levofloxacin, resulting in considerably lower blood levels. These agents should be taken at least two hours before or two hours after administration of Levofloxacin.
Theophylline
Although no interaction between levofloxacin and theophylline has been observed in a clinical study involving healthy volunteers, other quinolones could raise the plasma levels of theophylline and therefore theophylline plasma levels should be monitored when these two drugs are co-administered.
Dosage adjustment should be done when required.
Warfarin
Although no interaction between levofloxacin and warfarin has been observed in a clinical study involving healthy volunteers, patient coagulation tests should be monitored if these two drugs are co-administered. Elevations of the prothrombin time (INR) and episodes of bleeding have been reported in clinical use.
Cyclosporine and Digoxin
No significant clinical interaction between levofloxacin and these drugs has been observed in a clinical study involving healthy volunteers. Therefore, no dosage adjustment is required.
Probenecid and Cimetidine
If probenecid and cimetidine is co-administered, levofloxacin clearance is reduced and plasma levels are increased. However, these interactions do not warrant dosage adjustment for levofloxacin.
Non-Steroidal anti-inflammatory drugs
The concomitant administration of a non-steroidal anti-inflammatory drug with levofloxacin may increase the risk of CNS stimulation and convulsive seizures.
Antidiabetic agents
Instability of blood glucose, including hyperglycemia and hypoglycemia, may be observed in patients administered concomitantly with quinolones and oral antidiabetic agents. Therefore, blood glucose should be closely monitored .

DOSAGE AND ADMINISTRATION:
LEVOXIN could be taken before and after food intake.
Dosage in patients with normal renal function:
Dose diagram for LEVOXIN 500 mg Film Coated Tablet is shown below. The regular dose is 1 tablet containing 500 mg levofloxacin administered orally every 24 hours. This dose is applied to the patients having normal renal function (creatinine clearance > 80 ml/min).

Infection	Unit dose	Frequency once every	Duration of treatment	Total daily dose
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	24 hours	7 day	500 mg
Nosocomial Pneumonia	750 mg	24 hours	7-14 day	750 mg
Community Acquired Pneumonia	500 mg	24 hours	7-14 day	500 mg
Acute Maxillary Sinusitis	500 mg	24 hours	10-14 day	500 mg
Complicated Skin and Skin Structure Infections	750 mg	24 hours	7-14 day	750 mg
Uncomplicated Skin and Skin Structure Infections	500 mg	24 hours	7-14 day	500 mg
Chronic Bacterial Prostatitis	500 mg	24 hours	28 day	500 mg
Complicated Urinary Tract Infection	250 mg	24 hours	10 day	250 mg
Acute Pyelonephritis	250 mg	24 hours	10 day	250 mg
Uncomplicated Urinary Tract Infection	250 mg	24 hours	3 day	250 mg