Leflumax®
Levofloxacin 500 mg
Levofloxacin 750 mg

Coated tablets

MADE IN ARGENTINE Sale under prescription

Formula
Each LEFLUMAX® 500 mg coated tablet contains: Levofloxacin hemihydrate 512.46 mg (equivalent to 500 mg of levofloxacin). Excipients: polyvynilpyrrolidone K30 30.00 mg; microcrystalline cellulose 33.54 mg; sodium croscarmellose 15.00 mg; magnesium stearate 9.00 mg; Opadry II 85F 28751 17.94 mg; red iron oxide 0.06 mg.

Each LEFLUMAX® 750 mg coated tablet contains: Levofloxacin hemihydrate 768.60 mg (equivalent to 750 mg of Levofloxacin). Excipients: polyvynilpyrrolidone K30 50.00 mg; microcrystalline cellulose 116.40 mg; sodium croscarmellose 50.00 mg; magnesium stearate 15.00 mg; Opadry II 85F 28751 29.91 mg; red iron oxide 0.09 mg.

Therapeutical action
Broad-spectrum antibiotic with action against a wide variety of both aerobic and anaerobic Gram-negative and Gram-positive bacteria. Active against atypical microorganisms, such as *Chlamydia pneumoniae and Mycoplasma penumoniae.*
ATC CODE: J01MA12

Indications
Mild, moderate, and severe infections of the upper and lower respiratory tract in patients 18 years old and older, caused by susceptible microorganisms: acute maxillary sinusitis due to *Streptococcus pneumoniae, Haemophilus influenzae, or 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 *Staphylococcus aureus meti-S, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae;* adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is the documented or suspected pathogen, combination therapy with a beta-lactamic anti-pseudomonal agent is recommended; community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains, penicillin MIC not lower than 2 µg/mL), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pnemoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila,* or *Mycoplasma pneumoniae;* complicated skin and soft tissue infections due to *Staphylococcus aureus meti-S, Enterococcus faecalis, Streptococcus pyogenes,* or *Proteus mirabilis;* uncomplicated skin and soft tissue infections (mild to moderate), including 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 epidermidis;* complicated urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis,* or *Pseudomonas aeruginosa;* acute pyelonephritis (mild to moderate) caused by *Escherichia coli;* uncomplicated urinary tract infections (mild to moderate) due to *Escherichia coli, Klebsiella pneumoniae,* or *Staphylococcus saprophyticus;* mild and localized intraabdominal infections in association with an antibiotic effective against anaerobes; bacteraemia/septicaemia in patients with pneumonia or infections of the urinary tract, not as empirical treatment but in case of infections by levofloxacin-sensitive germs when other, narrower-spectrum antimicrobials prove ineffective.

Pharmacological characteristcs

Pharmacodynamics
Levofloxaxin is an antimicrobial agent from the quinolones group. The antibacterial activity of ofloxacin is mainly due to its Levo isomer. The mechanism of action of Levofloxacin, as well as other quinolones, involves the inhibition of DNA gyrase (topoisomerase II with bactericidal action), an enzyme required for the replication, transcription, repair, and recombination of DNA. The Levo isomer produces more hydrogen bonds, and therefore more stable complexes with DNA gyrase in the Dextro isomer. Microbiologically, this means an antibacterial activity 25 to 40 times higher of the Levo isomer –Levofloxacin– in comparison with the Dextro isomer.
Quinolones rapidly and specifically inhibit the synthesis of bacterial DNA.

Pharmacokinetics
Absorption: Levofloxacin is rapidly and completely absorbed after oral administration. Peak plasma concentrations are attained one to two hours after oral dosing. The absolute bioavailability following a 500 mg oral dose of Levofloxacin is approximately 99%. No clinically significant effect of food on levofloxacin absorption was observed. Therefore, Levofloxacin may be administered regardless of food intake. Levofloxacin pharmacokinetics are linear and predictable after single or multiple oral doses. After single oral doses of 250 to 1000 mg of levofloxacin, plasma concentrations increase proportionally to the dose.
Steady-state levels are reached within 48 hours following the administration of 500 mg once to twice daily. Stable maximum plasma concentrations reached after multiple oral doses once daily were approximately 5.7 and 0.5 µg/mL, respectively; after multiple oral doses administrated twice daily, concentrations were approximately 7.8 and 3.0 µg/mL, respectively.

Distribution: The mean volume of distribution of Levofloxacin generally ranges from 89 to 112 liters after single and multiple 500 mg doses, indicating widespread distribution in bodily tissues. Over a clinically significant range of Levofloxacin serum/plasma concentrations (1 to 10 mg/dL), the drug is approximately 24 to 38% bound to serum proteins in all species studied. In humans, levofloxacin is mainly bound to serum albumin. Levofloxacin binding to serum proteins is independent from the drug concentration.

Metabolism and elimination: Levofloxacin is stable in plasma and urine, and does not metabolize to its enantiomer, Dextrofloxacin. Levofloxacin undergoes limited metabolism in humans and is mainly excreted as unchanged drug in the urine.
Following oral administration, approximately 87% of the dose administered was recovered as unchanged drug in the urine within 48 hours, while less than 4% of the dose was recovered in the feces within 72 hours. Less than 5% of the dose administered was recovered in the urine as the desmethyl and N-oxide metabolites, the only metabolites identified in humans. These metabolites have little pharmacological activity.
The mean terminal elimination half-life of Levofloxacin in plasma ranges from approximately 6 to 8 hours following single or multiple doses of Levofloxacin.
Total average body clearance and renal clearance range from approximately 6 to 8 hours after single or multiple doses of levofloxacin.
The mean total body clearance and renal clearance range from approximately 144 to 226 mL/min, and from 96 to 142 mL/min, respectively.
Renal clearance in excess of the glomerular filtration rate suggests that tubular secretion of Levofloxacin occurs in addition to its glomerular filtration. Concomitant administration of either cimetidine or probenecid results in approximately 24% and 36% reduction in Levofloxacin renal clearance, respectively, indicating that secretion of Levofloxacin occurs in the renal proximal tubule.

Dosage and Mode of Administration
The usual dose for adults is 500 mg (1 coated tablet) to 750 mg (1 coated tablet and a half) every 24 hours.
The antibiotic may be administrated at any time of the day since food intake does not interfere with absorption.

Precautions and warnings
Use with extreme caution in patients with tendency to convulsive crises (with pre-existing injuries of the Central Nervous System) or under concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs, or with drugs that reduce the threshold of cerebral convulsive crises (e.g., theophylline). If pseudomembranous colitis is suspected, suspend therapy and establish suitable treatment. If tendinitis is suspected, suspend the medication immediately and initiate suitable treatment (for example, immobilization).
Among patients receiving quinolones, including ciprofloxacin, levofloxacin, ofloxacin, and moxifloxacin, there have been cases of tendon rupture in the shoulder, hand and especially the Achilles tendon, or others requiring surgery or resulting in prolongued incapacity.
Post-marketing pharmacovigilance reports indicate that this risk is increased in patients who have received or are receiving corticosteroid therapy, especially in those older than 65 years of age.
Product administration should be discontinued if the patient shows symptoms suggestive of tendinitis (pain, inflammation) or tendon rupture. Patients should rest and refrain from exercising until a diagnosis of tendinitis or tendon rupture has been discarded.
Rupture may occur from 48 hours after treatment initiation with any of the drugs mentioned until after treatment completion.
Patients older than 65 years of age are at greater risk of developing severe tendon conditions, including rupture, when treated with any of the quinolones mentioned before.
This risk increases in patients who were or are under treatment with corticosteroids.
Ruptures usually affect the Achilles tendon, or the tendons in hands or shoulders, and may occur during the antibiotic therapy or several months after treatment completion. Patients should be warned about this adverse effect; drug administration should be discontinued in case of any of these symptoms, and the patient should contact the physician immediately.
There have been cases of severe and ocassionally fatal hypersensitivity and/or anaphylactic reactions (which may occur after the first dose or after multiple doses); therefore, the medication should be suspended immediately at the first sign and support measures should be instituted. The patient should be adequately hydrated. Dose adjustment is required for patients with renal failure. Avoid strong sunlight or artificial UV light exposure. Prolongued use may result in overinfection. Precaution should be warranted in patients with renal failure or with actual or latent glucose-6-phosphate dehydrogenase defficiency. A strict control of diabetic patients concomitantly treated with an oral hypoglycaemiant agent or insulin is recommended, since there have been reports of glycemia disorders. Precaution is required when handling or using machinery.
If symptoms persist or are accompanied by other symptoms, consult your doctor.
If you are taking any other medicine, are pregnant or nursing, consult your doctor before taking this medicine.
If symptoms persist or other symptom accompany, consult your doctor.

Adverse reactions
Side Effects: *Comun:* Nausea, diarrhea, increased hepatic enzymes. Ocassional: Pruritus, rash, anorexia, vomiting, abdominal pain, dyspepsia, headache, dizziness/vertigo, somnolence, insomnia, increased serum bilirrubin and creatinine, eosinophilia, leukopenia, asthenia, fungal overgrowth and proliferation of other resistant microorganisms. Rare: Urticaria, bronchospasm/dyspnea, bloody diarrhea, depression, anxiety, psychotic reactions, paraesthesia, fear, agitation, confussion, convulsions, tachycardia, hypotension, arthralgia, myalgia, tendon disorders including tendinitis, neutropenia, thrombocytopenia. *Very rare:* Angioedema, hypotension, anaphylactic shock, photosensitization; hypoglycemia, especially in diabetic patients; hypoesthesia, visual and auditive alterations, taste and smelling perversion; (anaphylactic/anaphylactoid) shock; tendon rupture (for example, Achilles tendon), muscle weakness (it could be especially important in patients with myasthenia gravis); hepatic reactions such as hepatitis, acute renal failure; agranulocytosis; allergic pneumonitis, fever; extrapyramidal symptoms and other muscle coordination disorders, vasculitis due to hypersensitivity, porphyria attacks in patients already suffering from this disease. *Isolated cases:* Severe bullous eruptions (such as Stevens Johnson's syndrome), toxic epidermal necrolysis (Lyell's syndrome), and multiform exudative erythema, prolongation of the QT interval, rhabdomyolysis, hemolytic anemia, pancytopenia. There were also reports of abnormal EEG, encephalopathy, vasodilation, multiorganic failure, torsades de pointes, increased prothrombin time, and dysphonia.

Interactions
Theophylline, fenbufen, or similar non-steroidal anti-inflammatory drugs. Probenecid and cimetidine. Cyclosporine. Vitamin K antagonists, warfarin. Antidiabetic drugs. Tablet absorption is affected by iron salts, magnesium- or aluminum-containing antacids, and sucralfate. It may cause false negative results in the bacteriological diagnosis of tuberculosis.

Contraindications
Hypersensitivity to levofloxacin, other quinolones, or any excipient of the product; epilepsy; history of tendon problems due to administration of fluoroquinolones; children and adolescents; pregnancy and lactation.

Pregnancy and lactancy
Contraindicated during pregnancy and lactation.

Pediatric Use
Contraindicated in children and adolescents (younger than 18 years of age).

Overdosage
In case of accidental overdose, see your doctor immediately or contact a toxicology center.

How supplied
LEFLUMAX® 500 mg: Package containing 7 coated tablets.
LEFLUMAX® 750 mg: Package containing 5 coated tablets.

Information for patient
Read the package insert carefully before taking the product. Levofloxacin is available under medical prescription for the treatment of infectious processes caused by some bacteria. Keep the package insert, as it contains information that you may need to read again.
You should consult your doctor if symptoms do not improve or worsen.
Avoid excessive alcohol intake while taking the antibiotic.
If you have kidney stones, consult your doctor or pharmacist before using the product.
If symptoms persist, consult your doctor.
If you miss a dose, take it as soon as possible, but remember to wait for 24 hours before taking the next tablet.
Never double the dose.

Storage and conservation conditions
Keep at no more than 30 °C in its original package

Medicinal speciality authorized by Ministry of Heath. Certificate Nº 53.094
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Laboratorio ELEA PHOENIX