Nevotic
Levofloxacin

Composition:

Nevotic 250mg: Each film coated tablet contains 250mg levofloxacin corresponding to 512.46 mg of levofloxacin hemihydrate.

Nevotic 500mg: Each film-coated tablet contains 500mg levofloxacin corresponding to 256.23 mg of levofloxacin hemihydrate.

Pharmacological properties:

Levofloxacin is a synthetic antibacterial fluoroquinolone for oral use. As a fluoroquinolone antibacterial agent, levofloxacin inhibits bacterial DNA synthesis by acting on the DNA gyrase complex and topoisomerase IV. Levofloxacin is highly bactericidal in vitro. Its spectrum covers many Gram-positive and Gram-negative bacteria such as staphylococci, streptococci including pneumococci, enterobacteriaceae, haemophilus influenzae, non-fermentative Gram-negative bacteria and atypical microorganisms. There is generally no-cross resistance between levofloxacin and other classes of antibacterial agents. Nosocomial infections due to Pseudomonas aeruginosa may require combination therapy.

Following oral administration, levofloxacin is rapidly absorbed. The absolute bioavailability is approximately 100%. Food has little effect on the absorption of levofloxacin. Approximately 30-40% of levofloxacin are bound to serum protein. Steady state is achieved within 3 days. Penetration into bone tissue, blister fluid, and lung tissue is good but is poor into cerebro-spinal fluid. Levofloxacin is metabolized to a very small extent, the two metabolites account for <5% of the dose excreted in urine. Levofloxacin is eliminated relatively slowly from the plasma (t1/2: 6-8 h). Excretion is primarily by the renal route (>85% of the administered dose). With decreasing renal function, renal elimination and clearance are decreased and elimination half-lives increased (for a creatinine clearance comprised between 20-40 ml/min, t1/2 is 27 hours).

Indications:
Nevotic is indicated for the treatment of the following infections due to levofloxacin-susceptible microorganisms:
- Acute sinusitis,
- Acute exacerbation of chronic bronchitis,
- Community-acquired pneumonia,
- Complicated urinary tract infections including pyelonephritis,
- Skin and soft tissue infections,
- Prostatitis.

**Dosage and Administration:**

Dosage, duration of treatment and route of administration in adults with normal renal function (creatinine clearance >50 ml/min):
- Acute sinusitis: 500mg once daily for 10 to 14 days by oral route,
- Acute exacerbation of chronic bronchitis: 250 to 500mg once daily for 7 to 10 days by oral route,
- Community-acquired pneumonia: 500 mg once or twice daily for 7 to 14 days by oral route,
- Complicated urinary tract infections including pyelonephritis: 250mg once daily for 7 to 10 days by oral route. In cases of severe infection, consideration should be given to increasing the dose
- Skin and soft tissue infections: 250mg once daily or 500mg once or twice daily for 7 to 14 days by oral route,
- Prostatitis: 500mg once daily for 28 days by oral route.

Dosage in adult patients with impaired renal function (creatinine clearance ≤50 ml/min)

According to the severity of the infection, three treatment regimens are recommended depending on the creatinine clearance:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dosage regimen</th>
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<tr>
<td>50-20 ml/min.</td>
<td>First dose: 250mg Then 125mg/24h</td>
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<tr>
<td>19-10 ml/min.</td>
<td>First dose: 250mg Then 125mg/48h</td>
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Special populations
No dosage adjustment is required in patients with impaired liver function.

No dosage adjustment is necessary in elderly patients. However, special attention to renal function should be paid in elderly patients, and the dosage should be adapted accordingly.

Method of administration
- Nevotic tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dosage. The tablets may be taken during meals or between meals.

Overdose:
In case of overdose, contact immediately your physician.

According to toxicity studies in animals, the most important signs to be expected following acute overdose of levofloxacin are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, gastro-intestinal reactions such as nausea and mucosal erosions.

In clinical pharmacology studies performed with a supra-therapeutic dose increase in QT interval has been seen.

In the event of overdose the patient should be carefully observed (including ECG monitoring) and symptomatic treatment should be implemented. In case of acute oral overdose, gastric lavage should also be considered and 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.

Contraindications:
Nevotic is contraindicated:
• In patients hypersensitive (allergic) to levofloxacin, other quinolones or to any of its excipients,
• In patients with epilepsy,
• In patients with history of tendon disorders related to fluoroquinolone administration,
• In children or adolescents,
• During pregnancy and in breast-feeding women.

Side Effects:
The following undesirable effects may occur with the use of Nevotic:
• Gastrointestinal system: Common: Nausea, diarrhea; Uncommon: Anorexia (loss of appetite), vomiting, dyspepsia (upset stomach), abdominal pain; Rare: bloody diarrhea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (severe bowel inflammation); Very rare: Hypoglycemia (reduction in blood sugar) particularly in diabetic patients.
• Skin and allergic reactions: Uncommon: Rash, pruritus (itching); Rare: Urticaria (skin itching eruption), bronchospasm/dyspnea (difficulty in breathing); Very rare: Quincke's oedema (swelling of the face, tongue, throat or larynx), hypotension (reduced blood pressure), anaphylactic/oid shock (severe allergic reaction of sudden onset), photosensitization; Isolated cases of severe bullous eruptions such as Steven's Johnson syndrome (skin and mucous membrane bullous reactions), toxic epidermal necrolysis (Lyells' syndrome, i.e., bullous reactions) and erythema exudativum multiforme (red inflammatory rash with formation of blisters). Muco-cutaneous and anaphylactic/anaphylactoid reactions may sometimes occur even after the first dose.
• Nervous system: Uncommon: Headache, dizziness/vertigo, drowsiness and insomnia; Rare: Depression, anxiety, psychotic reactions (with e.g. hallucinations), paresthesia (abnormal sensations such as numbness, tingling and burning), tremor, agitation, confusion, convulsion; Very rare: Hypoesthesia (decreased sensitivity), visual and auditory disturbances, taste and smell disorders.
• Cardiovascular system: Rare: Tachycardia (rapid heart rate), hypotension; Very rare: Shock anaphylactic/anaphylactoid; Isolated cases: QT-interval prolongation (see section Overdose).
• Muscle and skeleton: Rare: Arthralgia (joint pain), myalgia (muscle pain), tendon disorders including tendonitis (inflammation of tendons, e.g. Achilles tendon); Very rare: Tendon rupture, muscular weakness which may be of special importance in patients
with myasthenia gravis (chronic progressive muscle disease); Isolated cases of rhabdomyolysis (dissolution of the muscle).

- Liver and kidney: Common: Increase in liver enzymes (transaminases ALT and AST); Uncommon: Increase in bilirubin and serum creatinine; Very rare: Hepatitis and acute kidney failure.
- Blood: Uncommon: Eosinophilia (increase in the number of certain white blood cells) and leucopenia (reduction in the number of white blood cells); Rare: Neutropenia (mild to severe reduction in the number of certain white blood cells) and thrombocytopenia (decrease in the number of platelets); Very rare: Agranulocytosis (insufficient number or absence of certain white blood cells); Isolated cases of hemolytic anemia (significant reduction in the number of red blood cells) and pancytopenia (pronounced reduction in the number of all blood cells).
- Others: Uncommon: asthenia (weakness), fungal overgrowth and proliferation of other resistant microorganisms; Very rare: Allergic pneumonitis (inflammation of the lung), fever. Other possible undesirable effects related to the class of fluoroquinolones: Very rare: Extrapyramidal symptoms and other disorders of muscular coordination, hypersensitivity vasculitis (inflammation of blood vessels) and attacks of porphyria (metabolic disease) in patients with porphyria.

Warnings and precautions:

- In patients predisposed to seizures, for example in case of simultaneous medications (see Interactions), and as with other quinolones, levofloxacin should be used with extreme caution.
- Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin, may be symptomatic of pseudomembranous colitis due to Clostridium difficile. If pseudomembranous colitis is suspected, levofloxacin must be stopped immediately.
- Tendonitis, rarely observed with quinolones, may occasionally lead to rupture involving Achilles tendon in particular. This undesirable effect may occur within 48 hours of starting of treatment and may be bilateral. Elderly patients are more prone to tendonitis. The risk of tendon rupture may be increased by coadministration of corticosteroids. If tendonitis is suspected, treatment with levofloxacin must be stopped IMMEDIATELY and the affected tendons must be put at rest.
• In patients with renal impairment, since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted.

• Although photosensitization is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays.

• As with other antibiotics, the use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during treatment, appropriate measures should be taken.

• Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents. This has to be taken into consideration when using levofloxacin.

Driving
Levofloxacin may cause undesirable effects such as dizziness, vertigo, drowsiness and visual disturbances, which may constitute a risk in situations such as driving a car or operating machinery.

Drug interactions:
In order to avoid possible interactions with other medicines, inform your physician or pharmacist about any other current treatment.

Tablets: There is no clinically relevant interaction with food. It is recommended that preparations containing divalent or trivalent cations such as iron salts or magnesium- or aluminum-containing antacids should not be taken 2 hours before or after levofloxacin administration, because of a possible reduction in absorption. The bioavailability of levofloxacin is significantly reduced when administered together with sucralfate, so it is recommended to administer sucralfate 2 hours after the levofloxacin administrations.

Tablets and solution for infusion: 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 theophyllin, fenbufen or similar non-steroidal anti-inflammatory drugs or other agents, which lower the seizure threshold.

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.
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.

**Use during pregnancy and lactation:**

Levofloxacin should not be used during pregnancy and lactation.

**Presentation:**

Nevotic 250mg: 7 film coated tablets per pack.
Nevotic 500mg: 7 film coated tablets per pack.