LEVOFLOXACIN HIKMA® Infusion

Levofloxacin

ACTION

Levofloxacin infusion is a synthetic antibacterial fluoroquinolone for intravenous use. As a fluoroquinolone antibacterial agent, levofloxacin inhibits bacterial DNA synthesis by acting on 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.

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 ($t_{1/2}$: 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, $t_{1/2}$ is 27 hours).

INDICATIONS

Levofloxacin 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

Strictly follow the recommended dosage unless directed otherwise by the physician.

The dosage and route of administration depend on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

Dosage, duration of treatment and route of administration in adults with normal renal function (creatinine clearance > 50 ml/min):

- *Acute sinusitis:* 500 mg once daily for 10 to 14 days by oral route
- *Acute exacerbation of chronic bronchitis:* 250 to 500 mg 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 or intravenous route.
- *Complicated urinary tract infections including pyelonephritis:* 250 mg once daily for 7 to 10 days by oral or intravenous route. In cases of severe infection, consideration should be given to increasing the dose by intravenous route.
- *Skin and soft tissue infections:* 250 mg once daily or 500 mg once or twice daily for 7 to 14 days by oral or intravenous route.
- *Prostatitis:* 500 mg once daily for 28 days by oral / intravenous 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:

Creatinine Clearance	Dosage regimen		
50-20 ml/min	First dose: 250 mg then 125 mg/24 h	First dose: 500 mg then 250 mg/24 h	First dose: 500 mg then 250 mg/12 h
19-10 ml/min	First dose: 250 mg then 125 mg/48 h	First dose: 500 mg then 125 mg/24 h	First dose: 500 mg then 125 mg/12 h
<10 ml/min (including hemodialysis and CAPD*)	First dose: 250 mg then 125 mg/48 h	First dose: 500 mg then 125 mg/24 h	First dose: 500 mg then 125 mg/24 h

* No additional doses are required after hemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD).

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

Levofloxacin infusion is only intended for SLOW intravenous infusion administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg and 60 minutes for 500 mg levofloxacin solution for infusion.

Preparation of infusion solution

Levofloxacin solution for infusion should be used IMMEDIATELY (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

CONTRAINDICATIONS

Levofloxacin 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.

WARNINGS AND PRECAUTIONS

- In patients predisposed to seizures, for example in case of simultaneous medications, 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 pseudo-membranous colitis due to *Clostridium difficile*. If pseudo-membranous colitis is suspected, levofloxacin must be stopped immediately.
- Tendinitis, 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 tendinitis. The risk of tendon rupture may be increased by coadministration of corticosteroids. If tendinitis 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 dehydrongenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents. This has to be taken into consideration when using levofloxacin.

Effects on ability to drive and use machines

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.

No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However, a pronounced lowering of the cerebral seizures threshold may occur when quinolones are given concurrently with theophylline, 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.

Incompatibilities/(compatibilities)

Levofloxacin solution for infusion should not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).

Levofloxacin solution for infusion is compatible with the following solutions for infusion: 0.9% sodium chloride solution, 5% dextrose injection, 2.5% dextrose in Ringer solution or combination solutions for parenteral nutrition (amino-acids, carbohydrates, electrolytes).

SIDE EFFECTS

Please tell your physician or pharmacist, if you experience any adverse effect with the use of this product.

Frequencies of undesirable effects: common (>1/100 and <1/10), uncommon (>1/1000 and <1/100), rare (>1/10 000 and <1/1000), very rare (<1/10 000), including isolated reports.

The following undesirable effects may occur with the use of Levofloxacin:

- **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, pruritis (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 to stimulation or sensations), 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.
- **Muscle and skeleton:** *Rare:* Arthralgia (joint pain), myalgia (muscle pain), tendon disorders including tendinitis (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 leukopenia (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. For infusion solution only: (common: Pain, reddening of the infusion site and phlebitis (inflammation of vein).

OVERDOSAGE

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.

STORAGE

Vials: Store below 25°C. Keep protected from light in the outer package. After removal of the outer packaging, keep the vial under indoor light conditions for maximum 3 days.

Infusion bags: Store below 25°C. Keep protected from light.

PRESENTATIONS

Vials

LEVOFLOXACIN HIKMA 250 mg:

Levofloxacin 250 mg in 50 ml/vial corresponding to 256.23 mg of levofloxacin hemihydrate.

LEVOFLOXACIN HIKMA 500 mg:

Levofloxacin 500 mg in 100 ml/vial corresponding to 512.46 mg of levofloxacin hemihydrate.

Excipients: sodium chloride, hydrochloric acid, water for injection.

Infusion bags

LEVOFLOXACIN HIKMA 250 mg:

Levofloxacin 250 mg in 50 ml/bag corresponding to 256.23 mg of levofloxacin hemihydrate.

LEVOFLOXACIN HIKMA 500 mg:

Levofloxacin 500 mg in 100 ml/bag corresponding to 512.46 mg of levofloxacin hemihydrate.

Excipients: sodium chloride, hydrochloric acid, water for injection.

Council of Arab Health Ministers, Union of Arab Pharmacists

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

Manufactured by
Hikma Farmacêutica, Portugal
For Hikma Pharmaceuticals,
Amman - Jordan

Keep medicament out of the reach of children

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