Bosch

For Medical Professional only

# ELOCIN

**Solution for IV Infusion**

500mg/100ml Infusion

**(Levofloxacin U.S.P.)**

(Product Specs.: M.S.)

ایلوسن

۵۰۰ ملی گرام/۱۰۰ ملی لیٹر انفیوژن

**DESCRIPTION:**
Levofloxacin (Elocin) is light yellowish-white to yellow-white crystals or crystalline powder, odorless and bitter taste. Light sensitive.
Chemically, it is (-) -(S)-9-flouro-2,3-dihydro-3-methyl-10-(4-methyl piperazinyl)-7-oxo-7H- pyrido [1,2,3-de][1,4] benzoxazine 6-carboxylic acid hemihydrate. The empirical formula is C18H20FN3O4 • ½ H2O and the molecular weight is 370.38

**CLINICAL PHARMACOLOGY:**
**PHARMACODYNAMIC PROPERTIES**
Pharmacotherapeutic group: Quinolone antibacterials – Fluoroquinolones ATC Code: J01MA12

**MECHANISM OF ACTION**
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 and other fluoroquinolone antimicrobials involves inhibition of bacterial topoisomerase IV and DNA gyrase (both of which are type II topoisomerases), enzymes required for DNA replication, transcription, repair and recombination.

**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 99 - 100 %.
Food has little effect on the absorption of levofloxacin.

**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.

**Penetration into tissues and body fluids:**
Levofloxacin has been shown to penetrate bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration into cerebro-spinal fluid.

**Metabolism:**
Levofloxacin is metabolized 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, 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.) There are no major difference in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

**Subject with renal insufficiency:**
The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below.

| CLcr (mL/min) | <20 | 20 - 40 | 50 - 80 |
|---|---|---|---|
| ClR (mL/min) | 13 | 26 | 57 |
| t1/2 (h) | 35 | 27 | 9 |

**Elderly subjects:**
There are no significant differences in levofloxacin kinetics between young and elderly subjects, except those associated with difference in clearance.

**Gender differences:**
Separate analysis for male and female subjects did not show clinical relevant gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

**THERAPEUTIC INDICATIONS:**
Levofloxacin 500 mg/100 ml solution for infusion is indicated in adults for the treatment.
- In Complicated skin and soft tissue infections / Complicated skin and skin structure infections Levofloxacin 500 mg/100ml should be used

only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- Community-acquired pneumonia
- Acute pyelonephritis and complicated urinary tract infections
- Chronic bacterial prostatitis.
- Inhalation Anthrax: postexposure prophylaxis and curative treatment.

Consideration should be given to official guidance on the appropriate use of anti-bacterial agents

**DOSAGE AND ADMINISTRATION:**
Levofloxacin 5 mg/ml solution for infusion is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen.

Dosage in patients with normal renal function (creatinine clearance >50mL/min)

| Indication | Daily dose regimen (according to severity) |
|---|---|
| Community-acquired pneumonia | 500mg once or twice daily |
| Pyelonephritis | 500mg once daily |
| Complicated urinary tract infections | 500mg once daily |
| Chronic bacterial prostatitis | 500mg once daily |
| Complicated skin and soft tissue infections | 500mg once or twice daily |
| Inhalation anthrax | 500mg once daily |

Impaired renal function (creatinine clearance ≤50ml/min)

| | Dose regimen | | |
|---|---|---|---|
| | **250mg/24h** | **500mg/24h** | **500mg/12h** |
| Creatinine clearance | first dose: 250mg | first dose: 500mg | first dose: 500mg |
| 50-20ml/min | then: 125mg/24h | then: 250mg/24h | then: 250mg/12h |
| 19-10ml/min | then: 125mg/48h | then: 125mg/24h | then: 125mg/12h |
| < 10 ml/min (including haemodialysis and CAPD) | then: 125mg/48h | then: 125mg/24h | then: 125mg/24h |

No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD)

**Impaired liver function**
No adjustment of dosage is required since levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.

**Elderly population**
No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

**Pediatric population**
Levofloxacin 5 mg/ml solution for infusion is contraindicated in children and growing adolescents.

**Method of administration**
Levofloxacin 500 mg/100 ml solution for infusion is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 60 minutes for 500 mg Levofloxacin solution for infusion.

**ADVERSE REACTIONS:**
**Common:** Insomnia, Headache, Dizziness, Diarrhea, Vomiting, Nausea, Increment in hepatic enzymes, Phlebitis.

**Uncommon:** Leukopenia, Eosinophilia, Anorexia, Anxiety, Confusional state, Nervousness, Somnolence, Tremor, Dysgeusia, Vertigo, Dyspnoea, Abdominal pain, Dyspepsia, Flatulence, Constipation, Blood bilirubin increased, Rash, Pruritus, Urticaria, Hyperhidrosis, Arthralgia, Myalgia, Blood creatinine increased, Asthenia, Fungal infection including Candida infection, Pathogen resistance.

**Rare:** Thrombocytopenia, Neutropenia, Angioedema, Hypersensitivity reactions, 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, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption, 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:** Pancytopenia, Agranulocytosis, Haemolytic anaemia,, Anaphylactic shock, Hyperglycaemia, Hypoglycaemic coma, Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt, Peripheral sensory neuropathy, Parsomia including ansomia, Dyskinesia ,Extrapyramidal disorder, Ageusia, Syncope, Benign intracranial hypertension, Hearing loss, Hearing impaired, Ventricular tachycardia which may result in cardiac arrest. Bronchospasm,Pneumonitis allergic, Diarrhoea – haemorhagic which in very rare cases may be indicative of enterocolitis including pseudomembranous colitis, Jaundice and severe liver injury, including cases with fatal acute liver failure, Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction, Leukocytoclasic vasculitis, Stomatitis, Rhabdomyolysis, Tendon rupture, Ligament rupture, Muscle rupture, Arthritis, Pain (including pain in back, chest and extremities).

**CONTRAINDICATIONS:**
Levofloxacin for infusion must not be used:
- in patients hypersensitive to levofloxacin or any other quinolone
- in patients with epilepsy
- in patients with history of tendon disorders related to fluoroquinolone administration
- in children or growing adolescents

**PRECAUTIONS AND WARNINGS:**
The use of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using

quinolone or fluoroquinolone containing products. treatment of these patients with levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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.

Inhalation Anthrax: use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax

The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg Levofloxacin 500mg/100ml solution for infusion should be observed. It is known for ofloxacin that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (L-isomer of ofloxacin) the infusion must be halted immediately.

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin.

Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin, (including several weeks after treatment) may be symptomatic of Clostridium difficile-associated disease (CDAD). 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 with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions, when treated with quinolone antibacterial agents Therefore, if levofloxacin has to be used in these patients, potential occurrence of hemolysis should be monitored.

Since levofloxacin is excreted mainly by the kidneys, the dose of Levofloxacin 5 mg/ml solution for infusion should be adjusted in patients with renal impairment.
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures or concomitant treatment with active substances that lower the cerebral seizure threshold, such as theophylline.

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis.

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. hypokalemia, hypomagne semia)
- 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.

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Levofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice

**USE IN PREGNANCY AND BREAST-FEEDING:**
**Pregnancy category: C**
There are limited amount of data from the use of levofloxacin in pregnant women. Elocin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Lactation:**
There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk levofloxacin must not be used in breast-feeding women.

**DRUG INTERACTION:**

**Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs**

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.

**Probenecid and cimetidine**

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

Caution should be exercised when levofloxacin is coadministered 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 coadministered with levofloxacin.

**Vitamin K antagonists**

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

**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 anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

**OVERDOSE:**

**Symptoms**

Following acute overdose of Levofloxacin solution for infusion signs of central nervous system symptoms might present such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.

**Management**

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

**Special precautions for disposal and other handling**

**Preparation for administration:**

Inspect the bag before use. It must only be used if the solution is a clear, greenish- yellow solution, practically free from particles.
No protection from light is necessary during infusion.
For single use only. Discard any unused solution.

**Mixture with other solutions for infusion:**

Levofloxacin 5 mg/ml solution for infusion is compatible with the following solutions for infusion:
sodium chloride 9 mg/ml (0.9%)
glucose 50 mg/ml (5%)
glucose 25 mg/ml (2.5%) in Ringer's solution
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Incompatibilities**

This medicinal product should not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate).
This medicinal product must not be mixed with other medicinal products

**DIRECTIONS:**

- Keep out of reach of children
- Protect from light, store at below 25°C.
- Do no refrigrate or freeze.
- For suspected adverse drug reaction for BOSCH products, report at ade@bosch-pharma.com

**WARNING:** To be sold on the prescription of registered medical practitioner only.

## ہدایات برائے استعمال:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
روشنی سے محفوظ ۲۵ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔
ریفریجریٹر میں رکھنے یا منجمد ہونے سے بچائیں
بچّوں کی پہنچ سے دُور رکھیں۔
انتباہ: صرف رجسٹرڈ میڈیکل پریکٹیشنر کے نسخے پر فروخت کے لئے۔

Manufactured by:
**Bosch Pharmaceuticals (Pvt) Ltd.**
209, Sector 23, Korangi Industrial Area,
Karachi - Pakistan

ISO 9001:2015 Certified Company