Starlev

(Levofloxacin)

COMPOSITION:

Starlev Tablets 250mg
Each tablet contains:
Levofloxacin ..... 250mg.
Finished Products Specs.: USP.

Starlev Tablets 500mg
Each tablet contains:
Levofloxacin ..... 500mg.
Finished Products Specs.: USP.

Starlev IV Infusion 500mg/100ml
Each 100ml vial contains:
Levofloxacin Hemihydrate (USP) Eq. to Levofloxacin 500mg
Finished Product Specs.: JP

DESCRIPTION:

Starlev (Levofloxacin) is a synthetic broad spectrum antibacterial agent for oral and intravenous administration. Chemically, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin. The chemical name is (-)-(S)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido [1,2,3,-de]-1,4 benzoxazine-6-carboxylic acid hemihydrate. The empirical formula is $C_{18}H_{20}FN_3O_4$.

CLINICAL PHARMACOLOGY:

Pharmacodynamics

Mechanism of Action:

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active substance ofloxacin. It acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Mechanism of Resistance:

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV.

Aerobic gram-positive microorganisms:

Bacillus anthracis, Staphylococcus aureus methicillin-susceptible, Staphylococcus saprophyticus, Streptococci, group C and G, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes.

Aerobic gram-negative microorganisms:

Eikenella corrodens, Haemophilus influenzae, Haemophilus para-influenzae, Klebsiella oxytoca, Moraxella catarrhalis, Pasteurella multocida, Proteus vulgaris, Providencia rettgeri.

Anaerobic microorganisms:

Peptostreptococcus.

Other microorganisms:

Chlamydophila pneumoniae, Chlamydophila psittaci, Chlamydia trachomatis, Legionella pneumophila, Mycoplasma pneumoniae, Mycoplasma hominis, Ureaplasma urealyticum.

Pharmacokinetics

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 h. The absolute bioavailability is approximately 99-100 %.
Steady state conditions are reached within 48 hours following a 500mg once or twice daily dosage regimen.
Food has little effect on the absorption of levofloxacin. Therefore, Levofloxacin can be administered without regard to food.
The plasma concentration profile of levofloxacin after I.V. administration is similar and comparable in extent of exposure (AUC) to that observed for Levofloxacin tablets when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.

Distribution:

Approximately 30-40 % of levofloxacin is bound to serum protein. The mean volume of distribution of levofloxacin is approximately 100L after single and repeated 500mg doses, indicating widespread distribution into body tissues.

Metabolism:

Levofloxacin not invert metabolically to its enantiomer, D-ofloxacin. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of an administered dose was recovered as unchanged drug in urine within 48 hours, whereas less than 4% of the dose was recovered in feces in 72 hours. Less than 5% of an administered dose was recovered in the urine as the desmethyl and N-Oxide metabolites, the only metabolites identified in humans.

Excretion:

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½ 6-8 h). Excretion is primarily by the renal route (> 85 % of the administered dose).

Special Population:

Renal insufficiency:
Clearance of levofloxacin is substantially reduced and plasma elimination half-life is substantially prolonged in patients with impaired renal function (creatinine clearance <50ml/min), requiring dosage adjustment in such patients to avoid accumulation. Neither haemodialysis nor continuous ambulatory peritoneal dialysis (CAPD) is effective in removal of levofloxacin from the body, indicating that supplemental doses of levofloxacin are not required following haemodialysis or CAPD.

Hepatic insufficiency:
Pharmacokinetic studies in hepatically impaired patients have not been conducted. Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Elderly:
There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects when the subjects' differences in creatinine clearance are taken into consideration. Levofloxacin dose adjustment based on age alone is not necessary.

THERAPEUTIC INDICATIONS:

Starlev (Levofloxacin) tablets are indicated in adults for the treatment of the following infections:

1. Acute bacterial sinusitis.
2. Acute exacerbation of chronic obstructive pulmonary disease including bronchitis.
3. Community-acquired pneumonia.
4. Complicated skin and soft tissue infections.

For the above-mentioned infections Levofloxacin tablets should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

5. Acute pyelonephritis and complicated urinary tract infections.
6. Chronic bacterial prostatitis.
7. Uncomplicated cystitis.
8. Inhalation Anthrax: postexposure prophylaxis and curative treatment.
9. Levofloxacin tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

POSOLOGY AND METHOD OF ADMINISTRATION:

Starlev tablets should be swallowed with sufficient amount of liquid. The tablets may be taken during meals or between meals. Starlev tablets should be taken about 2 hours before iron salts, antacids or sucralfate administration since reduction of absorption can occur.
Starlev Infusion should only be administered intravenously. It is not for intramuscular, intrathecal, intraperitoneal or subcutaneous administration. Infusion should be infused slowly over a period of not less than 60 minutes.
The dosage of Starlev (Levofloxacin) depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. The usual doses of Starlev are shown in the dosing chart.

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

Indications	Daily dose	Duration of Treatment
Acute bacterial sinusitis	500mg OD	10-14 days
Acute exacerbations of chronic obstructive pulmonary disease including bronchitis	500mg OD	07-10 days
Community-acquired pneumonia	500mg OD or Bid	07-14 days
Acute pyelonephritis	500mg OD	07-10 days
Complicated urinary tract infections	500mg OD	07-14 days
Uncomplicated cystitis	250mg OD	03 days
Chronic bacterial prostatitis	500mg OD	28 days
Complicated skin and soft tissue infections	500mg OD or Bid	07-14 days
Inhalation Anthrax	500mg OD	8 weeks

Note: Dosage may be adjusted according to the kind of infection and severity of the symptoms.

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

Creatinine Clearance	Dose regimen		
	Initial dose 250mg/24hr	Initial dose 500mg/24hr	Initial dose 500mg/12hr
50-20 ml/min	Then: 125mg/24h	Then: 250mg/24h	Then: 250mg/12h
19-10 ml/min	Then: 125mg/48h	Then: 125mg/24h	Then: 125mg/12h
Less than 10ml/min (haemodialysis and CAPD)	Then: 125mg/48h	Then: 125mg/24h	Then: 125mg/24h

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

ADVERSE REACTIONS:
Infections and infestations: Fungal infections including candida infection and pathogen resistance.
Blood and lymphatic system disorders: Eosinophilia, leukopenia, neutropenia, thrombocytopenia.
Immune system disorders: Angioedema and hypersensitivity.
Metabolism and nutrition disorders: Anorexia and hypoglycaemia (particularly in diabetic patients).
Psychiatric disorders:* Insomnia, confusional state, anxiety, nervousness, psychotic reactions (with e.g. hallucination, paranoia), depression, agitation, abnormal dreams and nightmares.
Nervous system disorders:* Headache, dizziness, somnolence, tremor, dysgeusia, convulsion and paraesthesia.
Eye disorders:* Visual disturbances such as blurred vision.
Ear and Labyrinth disorders:* Vertigo and tinnitus.
Cardiac disorders: Cardiac disorders and palpitation.
Vascular disorders: Hypotension.
Respiratory, thoracic and mediastinal disorders: Dyspnoea.
Gastrointestinal disorders: Diarrhoea, vomiting, nausea, abdominal pain, dyspepsia, flatulence and constipation.
Hepatobiliary disorders: Increased hepatic enzymes (ALT/AST, alkaline phosphatase, GGT) and increased blood bilirubin.
Skin and subcutaneous tissue disorder: Rash, pruritus, urticaria and hyperhidrosis.
Musculoskeletal and connective tissue disorder:* Arthralgia, myalgia, tendon disorders including tendinitis (e.g. Achilles tendon) and muscular weakness which may be of special importance in patients with myasthenia gravis.
Renal and urinary disorders: Increased blood creatinine and Acute renal failure (e.g. due to interstitial nephritis).
General disorders and administration site conditions:* Asthenia and pyrexia.
*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors.

WARNINGS AND PRECAUTIONS:
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.
Prolonged, disabling and potentially irreversible serious adverse drug reactions:
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.
Tendinitis and 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. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Levofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Peripheral Neuropathy:
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Levofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition.

CONTRAINDICATIONS:
Levofloxacin tablets must not be used in:
- Patients hypersensitive to the active substance or other quinolones or to any of its excipients.
- Patients with epilepsy.
- Patients with history of tendon disorders related to fluoroquinolone administration.
- Children or growing adolescents.
- Pregnancy.
- Breast-feeding women.

DRUG INTERACTIONS:
Antacids, Sucralfate, Metal Cations, Multivitamins: Concurrent administration of levofloxacin with antacids containing magnesium, or aluminum, as well as sucralfate metal cations such as iron and multivitamin preparations with zinc may interfere with the gastrointestinal absorption of levofloxacin resulting in systemic levels considerably lower than desired. These agents should be taken at least 2 hours before or 2 hours after levofloxacin administration.

Theophylline, Warfarin, Cyclosporine, Digoxin, Probenecid and Cimetidine: No significant effect of levofloxacin on the plasma concentrations, AUC, and other disposition parameters for theophylline, warfarin, cyclosporine, digoxin, probenecid and cimetidine was detected in a clinical study.

NSAIDs: The concomitant administration of a non-steroidal anti-inflammatory drug with a quinolone, including levofloxacin, may increase the risk of CNS stimulation and convulsive seizures.

Antidiabetic agents: disturbances of blood glucose, including hyperglycemia and hypoglycemia, have been reported in patients treated concomitantly with quinolones and an antidiabetic agent (e.g.,glyburide/glibenclamide) or insulin. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

OVERDOSAGE:
Levofloxacin exhibits a low potential for acute toxicity. In the event of an acute overdosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by haemodialysis or peritoneal dialysis.

PRESENTATION:
Starlev Tablets 250mg: Available in alu-alu Blister pack of 10 Tablets.
Starlev Tablets 500mg: Available in alu-alu Blister pack of 10 Tablets.
Starlev IV Infusion 500mg/100ml: Available in glass vial of 1's.

STORAGE:
Tablets:
- Store below 30°C.
- Protect from heat, light and moisture.

Infusion:
- Store below 30°C.
- Protect from heat and light.
- Do not refrigerate or freeze.

To be sold on the prescription of a registered medical practitioner only.

Keep all medicines out of the reach of children.

Manufactured by :
Indus Pharma (Pvt.) Ltd.
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