Levoson®

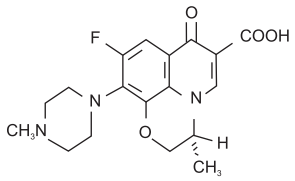
Levofloxacin

لیووسن®

(لیووفلاکساسن)

DESCRIPTION

Levson (Levofloxacin) is a synthetic broad-spectrum antibacterial agent Chemically, Levofloxacin, a chiral fluorinated carboxyquinolone is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin with a chemical name of: (-)-(S)-9-fluoro-2, 3-dihydro-3-methyl-10-(4-methyl-piperazinyl-7- oxo-7H-Pyrido [1,2,3,-de] [1,4] benzoxazine-6-carboxylic acid. The molecular formula is
$C_{18}H_{20}FN_3O_4$ and the structural formula is



COMPOSITION

Levoson® (Levofloxacin) is available for oral administration in film coated tablets as:

1 **Levoson®** Tablet 250mg
Each tablet contains:
Levofloxacin as Hemihydrate……250mg
2 **Levoson®** Tablet 500mg
Each tablet contains:
Levofloxacin as Hemihydrate……500mg
(Product contains Gluten/Lactose)

CLINICAL PHARMACOLOGY

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 main mechanism of action of levofloxacin involves the inhibition of DNA (gyrasetopoisomerase), which is essential in the reproduction of bacterial DNA. Levofloxacin has in-vitro activity against the following gram-negative and gram-, positive microorganisms. It is often bactericidal at concentrations equal to or sightly greater than inhibitory concentration.

Aerobic gram-positive micro-organisms

Enterococcus faecalis (moderately susceptible)
Staphylococcus aureus (methicillin-susceptible strains)
Staphylococcus saprophyticus
Streptococcus pneumoniae (including penicillin-resistant strains)
Streptococcus pyogenes

Aerobic gram-negative microorganisms

Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Haemophilus para influenzae
Klebsiella pneumonia
Legionella pneumophila
Salmonella species
Moraxella catarrhalis
Proteus mirabillis
Pseudomonas aeruginosa
(some strains of Pseudomonas aeruginosa may develop resistance rapidly during treatment with levofloxacin.)

Anaerobic microorganisms

Bacteroides fragilis
Clostridium perfringens
Peptostreptococcus

Other microorganisms

Chlamydia pneumonia
Mycoplasma pneumoniae

Pharmacokinetics

Absorption

Levofloxacin is rapidly and essentially completely absorbed after oral administration, peak plasma concentrations are attained 1-2 hours after oral dosing. The absolute bioavailability is approximately 99% demonstrating complete oral absorption of levofloxacin. Levofloxacin pharmacokinetics are linear and predictable after single and multiple dosing regimens. Steady state conditions are reached within 48 hours following a 500mg or 750mg once daily dosage regimens. The mean ±SD peak and trough plasma concentrations attained following multiple once-daily oral dosage regimens were approximately 5.7±1.4 and 0.5±0.2µg/ml after the 500mg doses, and 8.6±1.9 and 1.1±0.4µg/ml after the 750mg doses, respectively. Oral administration of a levofloxacin with food slightly prolongs the time to peak plasma concentration by approximately 1 hour and slightly decreases the peak plasma concentration by approximately 14%. Therefore, levofloxacin can be administered without regard to food.

Distribution

The mean volume of distribution generally ranges from 74-112 liters after single and multiple dosing of 500mg or 750mg doses. Levofloxacin is approximately 24 to 38% bound to serum proteins. Levofloxacin is mainly bound to serum albumin in humans. The binding of levofloxacin to serum proteins is independent of the drug concentration.

Metabolism and Elimination

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. These metabolites have little relevant pharmacological activity. The mean terminal elimination half-life (T1/2) of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin. The mean Apparent total body clearance and renal clearance range from approx. 144-726ml/min and 96-142ml/min respectively.

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

Levoson® (levofloxacin) tablets are indicated for the treatment of adults (>18 years of age) with mild, moderate, and severe infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

- Acute maxillary sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Community-acquired pneumonia and nosocomial pneumonia
- Typhoid & paratyphoid fever
- Complicated skin and skin structure infections
- Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections
- Complicated urinary tract infections (mild to moderate)
- Uncomplicated urinary tract infections (mild to moderate)
- Acute pyelonephritis (mild to moderate)

DOSAGE AND ADMINISTRATION

Levoson® (levofloxacin) tablets are administered once or twice daily. The dosage depends on the types and severity of the infections and the sensitivity of the presumed, causative pathogen. Levoson (levofloxacin) should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals.
Levoson® (levofloxacin) tablets should be administered at least two hours before or two hours after antacids containing magnesium, aluminium, as well as sucralfate, metal cations such as iron, and multivitamin preparations with zinc.
The dosage guidelines as per the infection are given as under

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

INDICATIONS	DAILY DOSE (mg)	DURATION (DAYS)
Acute Maxillary Sinusitis	250mg bid or 500mg od	10 - 14
Acute Bacterial Exacerbation of Chronic Bronchitis	250mg bid or 500mg od	7
Community Acquired Pneumonia and Nosocomial Pneumonia	250mg bid or 500mg od	7 - 14
	750mg od	5
Typhoid fever paratyphoid fever	250mg bid or 500mg od	10 - 14
Uncomplicated Skin and Soft Tissue Infections	250mg bid or 500mg od	7 - 10
Complicated Skin and Soft Tissue Infections	750mg od	7 - 14
Uncomplicated Urinary Tract Infections	250mg od	3
Complicated Urinary Tract Infections	250mg od	10
Acute Pyelonephritis	250mg od	10

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 750mg /24hr.
50-20 ml/min	No adjustment required	250mg /24hr	750mg /24hr
19 - 10ml/min	250mg /48hr	250mg /48hr	500mg /48hr.
Haemodialysis and CAPD	250mg /48hr	250mg /48hr	500mg /48hr.

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

ADVERSE REACTIONS

Levofloxacin is usually well tolerated. However, following are the adverse effects reported during its therapy.

General: allergic reactions (anaphylactic/anaphylactoid reaction) with symptoms such as urticaria, cramping of bronchi and possibly severe breathing problems, as well as in very rare cases swelling of the skin and mucous membranes.

Skin reactions and general skin reaction: Itching and rash.

Gastrointestinal tract/metabolism: Nausea and diarrhoea, loss of appetite, vomiting, pain in the abdomen region, dyspepsia, bloody diarrohea that in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis.

Nervous system: Headache, vertigo/dizziness, drowsiness, sleeping problems, paraesthesia e.g. like tingling in the hands, trembling, restlessness, anxiety, convulsions and confusions.

Cardiovascular system: Abnormal rapid beating of the heart, drop of blood pressure and circulatory (shock like) collapse.

Effects on muscles, tendon and bones: Tendon pain including inflammation, joint pain or muscle pain. Tendon rupture (Achilles Tendon), this side effect may occur within 48 hours after starting treatment and may be bilateral. Muscular weakness, which may be of special importance in patients with myasthenia gravis (a rare disease of nervous systems).

Liver and kidney: Increased levels of liver enzymes (e.g. ALT, AST) increased level of bilirubin and serum creatinine, inflammation of the liver, disturbance of kidney function up to kidney failure.

Effect on the blood: Increase of certain blood cells (eosinophillia) decrease in the number of white blood cells (leukopenia).

CONTRAINDICATIONS

Levofloxacin is contraindicated in patients with a history of hypersensitivity to this drug and/or other quinolones. Levofloxacin is contraindicated in children and adolescents as cartilage damages cannot be excluded.

PRECAUTIONS

General

- Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of highly concentrated urine.
- As with other quinolones, levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose seizures or lower the seizure threshold.
- Moderate to severe phototoxicity reactions have been observed in patients exposed to direct sunlight while receiving drugs in this class. Excessive exposure to sunlight should be avoided. Therapy should be discontinued if phototoxicity (skin eruptions) occurs.
- Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity.
- Levofloxacin should be discontinued if the patient experiences pain, inflammation or rupture of a tendon during therapy.
- As with any potent antimicrobial drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic is advisable during therapy.

Renal Insufficiency

Levofloxacin should be administered with caution in the presence of renal insuffciency. Careful clinical observation and appropriate laboratory studies should be performed prior to and during therapy since elimination of levofloxacin may be reduced. In patients with impaired renal function (creatinine clearance <50ml/min) adjustment of the dose regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance.

Paediatric use

Safety and effectiveness of levofloxacin in individuals below 18 years of age have not been established.

Pregnancy

There are no adequate and well-controlled studies in pregnant women. Levofloxacin should be used during pregnancy only if the potential benefit justified the potential risk to the fetus.

Nursing Mothers

Levofloxpcin has not been measured in human milk. Based upon data from ofloxacin, it can be presumed that levofloxacin will be excreted in human milk. Because of the potential for serious adverse reactions from levofloxacin in nursing infants, nursing should not be undertaken by mothers who must use levofloxacin.

Drug Interactions

Antacids, Sucralfate, Metal Cations, Multivitamins: Concurrent administration of levofloxacin with antacids containing magnesium, or aluminium; 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 clinical study.

Non-steroidal anti-inflammatory drugs: 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 gulcose, 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 patients should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by haemodialysis or peritoneal dialysis.

How Supplied

Levoson® (Levofloxacin) Tablets 250mg are available in Alu. Alu. Pack of 10 Tablets.
Levoson®(Levofloxacin) Tablets 500mg are available in Alu. Alu. Pack of 10 Tablets.

Dosage:

As prescribed by the physician.

Instructions:

Store in a dry place below 30°C and protect from sunlight.
Keep all medicines out of reach of children.
To be sold on prescription of a registered medical practitioner only.

خوراک:

ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات:

خشک جگہ پر ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں۔

سورج کی روشنی سے بچائیں۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

صرف رجسٹرڈ ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by:
Dyson Research Laboratories (Pvt) LTD.
28th-KM Ferozepur Road, Lahore,Pakistan.
ISO 9001:2015 Certified Company