READ INSTRUCTION CAREFULLY BEFORE USE . ASK YOUR DOCTOR FOR FURTHER INFORMATION. USE AS DIRECTED BY DOCTOR ONLY.

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LOXOF

(Levofloxacin Tablets 500 mg)

Specification : In-house

COMPOSITION

LOXOF 250 mg

Each film-coated tablet contains:
Levofloxacin hemihydrate
equivalent to Levofloxacin 250 mg

LOXOF 500 mg

Each film-coated tablet contains:
Levofloxacin hemihydrate
equivalent to Levofloxacin 500 mg

INACTIVE INGREDIENTS

Microcrystalline Cellulose, Polysorbate 80, Hypromellose, Opadry, Crospovidone, Magnesium Stearate.

DESCRIPTION

Levofloxacin is a synthetic broad spectrum antibacterial agent. It is a chiral fluorinated carboxyquinolone and the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacine. It is chemically designated as (-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4- benzoxacine -6-carboxilic acid hemihydrate.

The empirical formula for Levofloxacin is $C_{18}H_{20}FN_3O_4 \cdot 1/2H_2O$ and its molecular weight is 370.38.

PHARMACOLOGY[1]

Mechanism of action

Levofloxacine is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations. The mechanism of action of levofloxacin and other fluoroquinolone antimicrobials involves inhibition of DNA gyrase (bacterial topoisomerase II), an enzyme required for DNA replication, transcription, repair and recombination.

Pharmacokinetics

Levofloxacin is rapidly and essentially completely absorbed after oral administration. Peak plasma concentrations are usually attained one to two hours after oral dosing. The absolute bioavailability of a 500 mg oral dose of levofloxacin is approximately 99 %. Levofloxacin pharmacokinetics are linear and predictable after single and multiple oral dosing regimens.

Levofloxacin can be administered without regard to food.

Levofloxacin is widely distributed into body tissues. Penetration of levofloxacin into blister fluid is rapid and extensive. Levofloxacin also penetrates well into lung tissues. Lung tissue concentrations are generally 2 to 5 fold higher than plasma concentrations. In vitro, over a clinically relevant range (1 to 10 µg/ml) of serum/plasma levofloxacin concentrations, levofloxacin is approximately 24 to 38% bound to serum proteins across all species studied. Levofloxacin undergoes limited metabolism in humans and is primarily excreted as unchanged drug in the urine. Following oral administration, approximately 87% of administered dose is recovered as unchaged drug in urine within 48 hours, whereas less than 4% of the dose is recovered in feces in 72 hours. Less than 5% of an administered dose is 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 plasma elimination half-life of levofloxacin ranges from approximately 6 to 8 hours following single or multiple doses of levofloxacin.

The plasma concentration profile levofloxacin after IV administration is similar and comparable in extent of exposure (AUC) to that observed for oral levofloxacin when equal doses (mg/mg) are administered. Therefore, the oral and IV routes of administration can be considered interchangeable.

Special Populations

Renal insufficiency

Clearance of levofloxacin is reduced and plasma elimination half-life is prolonged in patients with impaired renal function (creatinine clearance < 80 ml/min), requiring dosage adjustment in such patients to avoid accumulation. Neither hemodialysis 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 hemodialysis or CAPD.

Hepatic insufficiency

Due to the limited extent of levofloxacin metabolism, the pharmacokinetics of levofloxacin are not expected to be affected by hepatic impairment.

Antimicrobial spectrum

Levofloxacin has *in vitro* activity against a wide range of gram-negative and gram-positive microorganisms. Levofloxacin is often bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Although cross-resistance has been observed between levofloxacin and some other fluoroquinolones, some microorganisms resistant to other fluoroquinolones may be susceptible to levofloxacin.

Levofloxacin has been shown to be active against most strains of the following microorganisms both *in vitro* and in clinical infections.

Aerobic gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains), *Staphylococcus saprophyticus*, *Streptococcus pneumoniae* (including penicillin-resistant strains), *Streptococcus pyogenes*.

Aerobic gram-negative microorganisms

Enterobacter cloacae, *Legionella pneumophila*, *Escherichia coli*, *Moraxella catarrhalis*, *Haemophilus influenzae*, *Proteus mirabilis*, *Haemophilus parainfluenzae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*.

Other microorganisms

Chlamydia pneumoniae, *Mycoplasma pneumoniae*.

The following *in- vitro* data are available, but their clinical significance is unknown.

Levofloxacin exhibits *in-vitro* minimum inhibitory concentrations (MIC values) of 2 µg/ml or less against most (90%) strains of the following microorganisms, however the safety and effectiveness of levofloxacin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Aerobic gram-positive microorganisms

Staphylococcus epidermidis, *Streptococcus* (Group B)(methicillin-susceptible strains), *Streptococcus agalactes*, *Streptococcus* (Group C/F), Viridans group streptococci.

Aerobic gram-negative microorganisms

Acinetobacter baumannii, *Klebsiella oxytoca*, *Acinetobactor calcoaceticus*, *Morganella morganii*, *Acinetobacter lwoffii*, *Pantoea (Enterobacter) agglomerans*, *Bordetella pertussis*, *Proteus vulgaris*, *Citrobacter (diversus) koseri*, *Providencia rettgeri*, *Citrobacter freundii*, *Providencia stuartii*, *Enterobater aerogenes*, *Pseudomonas fluorescens*, *Enterobacter sakazakii*, *Serratia marcescens*.

Anaerobic gram-positive microorganisms

Clostridium perfringens.

CLINICAL STUDIES[1]

Adult inpatients and outpatients with a diagnosis of community-acquired bacterial pneumonia have been evaluated in two pivotal clinical studies. In the first study, patients were enrolled in a prospective, multi-center, unblinded randomized trial comparing levofloxacin 500 mg once daily orally or intravenously for 7 to 14 days to ceftriaxone 1 to 2 grams intravenously once or in equally divided doses twice daily followed by cefuroxime axetil 500 mg orally twice daily for a total of 7 to 14 days.

Patients assigned to treatment with the control regimen were allowed to receive erythromycin (or doxycycline if intolerant of erythromycin) if an infection due to atypical pathogens was suspected or proven. Clinical and microbiologic evaluations were performed during treatment, 5 to 7 days post-therapy, and 3 to 4 weeks post-therapy. Clinical success (cure plus improvement) with levofloxacin at 5 to 7 days post-therapy, the primary efficacy variable in this study, was superior (95%) to the control group (83%). In the second study, patients were enrolled in a prospective, multi-center, non-comparative trial of 500 mg levofloxacin administered orally or intravenously once daily for 7 to 14 days. Clinical success for clinically evaluable patients was 93%. For both studies, the clinical success rate in patients with atypical pneumonia due to *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila* were 96%, 96% and 70%, respectively.

	Microbiologic Eradication Rates Across Both Studies	
Pathogen	**No. Pathogens**	**Microbiologic Eradication Rate (%)**
H. influenzae	55	98
S. pneumoniae	83	95
S. aureus	17	88
M. catarrhalis	18	94
H. parainfluenzae	19	95
K. pneumoniae	10	100

Additional studies were initiated to evaluate the utility of levofloxacin in community-acquired pneumonia due to *S. pneumoniae*, with particular interest in penicillin-resistant strains (MIC value for penicillin² ≥ 2 µg/ml). In addition to the studies previously discussed, inpatients and outpatients with mild to severe community-acquired pneumonia were included in six additional clinical studies; one double- blind study, two open label randomized studies, and three open label non-comparative studies. The clinical success rate (cured or improved) among the levofloxacin-treated patients with S. pneumoniae was 98%. Across these 8 studies, all of the evaluable levofloxacin-treated patients with community-acquired pneumonia due to penicillin-resistant S. pneumoniae achieved clinical success (cure or improvement).

INDICATIONS[1]

LOXOF is indicated for the treament of adults (≥ 18 years of age) with mild, moderate and severe infections caused by levofloxacin-susceptible microorganisms:

- Acute maxillary sinusitis
- Acute bacterial exacerbation of chronic bronchitis
- Community - acquired pneumonia
- Uncomplicated skin and skin structure infections (SSSI)(mild to moderate)
- Complicated urinary tract infections (mild to moderate)
- Acute pyelonephritis (mild to moderate)
- Uncomplicated urinary tract infections (mild to moderate)

DOSAGE AND ADMINISTRATION[2,3]

The usual dose of levofloxacin is 500 mg orally every 24 hours as described in the table below. These recommendations apply to patients with normal renal function (i.e., CL_{cr} ≥ 80 ml/min) for patients with altered renal function (i.e., CL_{cr} ≤ 80 ml/min) **see Patients with Impaired Renal Function. LOXOF** tablets may be taken during meals or between meals. Oral doses should be administered at least two hours before or two hours after antacids containing magnesium, or aluminum, as well as sucralfate, metal cations such as iron, and multi -vitamin preparations with zinc.

Patients with Normal Renal Function

Infection	Unit dose	Frequency	Duration	Daily Dose
Acute Bacterial Exacerbation of Chronic Bronchitis	500 mg	q24h	7 days	500 mg
Community Acquired Pneumonia	500 mg	q24h	7 - 14 days	500 mg
Acute Maxillary Sinusitis	500 mg	q24h	10 - 14 days	500 mg
Uncomplicated SSSI	500 mg	q24h	7 - 10 days	500 mg
Complicated UTI	250 mg	q24h	10 days	250 mg
Acute pyelonephritis	250 mg	q24h	10 days	250 mg
Uncomplicated UTI	250 mg	q24h	3 days	250 mg

Patients with Impaired Renal Function

Renal Status	Initial Dose	Subsequent Dose
Acute Bacterial Exacerbation of Chronic Bronchitis/Community Acquired Pneumonia/ Acute Maxillary Sinusitis/Uncomplicated SSSI		
CL_{cr} from 50 to 80 ml/min	No dosage adjustment required	
CL_{cr} from 20 to 49 ml/min	500 mg	250 mg q24h
CL_{cr} from 10 to 19 ml/min	500 mg	250 mg q48h
Hemodialysis*	500 mg	250 mg q48h
CAPD*	500 mg	250 mg q48h
Complicated UTI/Acute Pyelonephritis		
CL_{cr} ≥ 20 ml/min	No dosage adjustment required	
CL_{cr} from 10 to 19 ml/min	250 mg	250 mg q48h
Uncomplicated UTI	No dosage adjustment required	

CL_{cr} = creatinine clearances

CAPD - chronic ambulatory peritoneal dialysis

* - No additional doses are required after hemodialysis or CAPD.

PRECAUTIONS[1,2]

- **General**

Although levofloxacin is more soluble than other quinolones, adequate hydration of patients receiving levofloxacin should be maintained to prevent the formation of a highly concentrated urine.

Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp, solarium), in order to prevent photosensitisation.

Some quinolones have been associated with prolongation of the QT interval on the electrocardiogram and infrequent cases of arrhythmia. Extremely rare cases of torsades de pointes, have been reported in patients taking levofloxacin. These reports generally involve patients who had other concurrent medical conditions and the relationship to levofloxacin has not been established. Among drugs known to cause prolongation of the QT interval, the risk of arrhythmias may be reduced by avoiding use in the presence of hypokalemia, significant bradycardia, or concurrent treatment with class Ia or class III antiarrhythmic agents.

- **Warnings**

Convulsions and toxic psychoses have been reported in patients receiving quinolones, including levofloxacin. Quinolones may also cause increased intracranial pressure and central nervous system stimulation. These reactions may occur following the first dose. If these reactions occur in patients receiving levofloxacin, the drug should be discontinued and appropriate measures instituted. As with other quinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g. severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g. certain drug therapy, renal dysfunction) (See **Drug Interactions**)

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with quinolones, including levofloxacin. These reactions often occur following the first dose. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity. Serious acute hypersensitivity reactions may require treatment with epinephrine and other resuscitative measures, including oxygen, intravenous fluids, antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including levofloxacin, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent.

If pseudomembranous colitis is suspected, levofloxacin must be stopped immediately and patients should be treated with supportive measures, specific therapy without delay (e.g. oral vancomycin). Products inhibiting the peristalsis are contraindicated in this clinical situation.

Ruptures of the shoulder, hand, or Achilles tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving quinolones, including levofloxacin. Levofloxacin should be discontinued if the patient experiences pain, inflammation, or rupture of a tendon. Patients should rest and retrain from exercise until the diagnosis of tendinitis or tendon rupture has been confidently excluded. Tendon rupture can occur during or after therapy with quinolones, including levofloxacin.

- **Contraindications**

LOXOF is contraindicated in persons with a history of hypersensitivity to levofloxacin, quinolone antimicrobial agents, or any other components of this product.

- **Pregnancy**

Levofloxacin should be used during pegnancy only if the potential benefit justifies the potential risk to the fetus.

- **Lactation**

Levofloxacin 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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

- **Pediatrics**

Safety and effectiveness in children and adolescents below the age of 18 years have not been established.

- **Geriatrics**

No overall differences in safety or effectiveness have been observed between subjects > 65 years and younger subjects, and other reported clinical experience has not identified differences in reponses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

- **Carcinogenicity/ Mutagenicity/ Impairment of fertility**

In a long term carcinogenicity study in rats, levofloxacin exhibited no carcinogenic or tumongenic potential following daily dietary administration for 2 years, the highest dose was 2 or 10 times the recommended human dose based on surface area or body weight, respectively .

Levofloxacin was not mutagenic in the following assays: Ames bacterial mutation assay (S. typhimurium and E. coli), CHL/HGPRT forward mutation assay, mouse micronucleus test, mouse dominant lethal test, rat unscheduled DNA synthesis assay, and the mouse sister chromatid exchange assay. It was positive in the *in vitro* chromosomal aberration (CHL cell line) and sister chromatid exchange (CHL/IU cell line) assays.

Levofloxacin caused no impairment of fertility or reproductive performance in rats at oral doses as high as 360 mg/kg/ day (2124 mg/m²), corresponding to 3.0 or 18 times the recommended maximum human dose based on surface area or body weight, respectively, and intravenous doses as high as 100 mg/kg/day (590 mg/m²), corresponding to 10 or 5 times the recommended maximum human dose based on surface area or body weight, respectively.

- **Drug Interactions**

Antacids, sucralfate, metal cations, multi-vitamins : concurrent administration of levofloxacin with antacids containing magnesium, or aluminium, as well as sucralfate, metal cations such as iron, and multi-vitamin 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 two hours before or two hours after levofloxacin administration.

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs : No pharmacokinetic interactions of levofloxacin have been found with theophyline in a clinical study. However, 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. Levofloxacin concentrations are about 13% higher in the presence of fenbufen than when administered alone.

Calcium carbonate, digoxin, ranitidine, warfarin : the pharmacokinetics of levofloxacin are not affected to any clinically relevant extent when levofloxacin is administered together with any of these drugs.

Probenecid and cimetidine : No significant effect of probenecid or cimetidine on the rate and extent of levofloxacin absorption was observed in a clinical study involving healthy volunteers.

Antidiabetic agents: Disturbances of blood glucose, including hyperglycemia and hypoglycemia have been reported in patients treated concomitantly with quinolones and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co-administered.

- **Adverse reactions**

Levofloxacin is generally well tolerated. Commonly reported side effects may include nausea, diarrhoea and increases in liver enzymes (e.g. ALT/AST).

Less commonly, pruritus, rash, anorexia, vomiting, abdominal pain, dyspepsia, headache, dizziness/vertigo, drowsiness, insomnia, increase in bilirubin, increase in serum creatinine, eosinophilia, leukopenia, asthenia, fungal overgrowth and proliferation of other resistant microorganisms have been reported.

Rarely occuring side effects may include urticaria, bronchospasm/dyspnoea, bloody diarrhoea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, paraesthesia, tremor, anxiety, agitation, confusion, convulsion, tachycardia, hypotension, arthralgia, myalgia, tendon disorders including tendinitis (e.g. Achilles tendon), neutropenia, thrombocytopenia. In very rare situations, angio-oedema, anaphylactic-like shock, photosensitisation, hypoglycaemia, particularly in diabetic patients, hypoaesthesia, visual and auditory disturbances, disturbances of taste and smell, hallucinations, muscular weakness, liver reactions, such as hepatitis, acute kidney failure (e.g. due to interstitial nephritis), agranulocytosis, allergic pneumonitis, liver failure have been observed.

Isolated cases of severe bullous eruptions such as Stevens Johnson syndrome, toxic shock, epidermal necrolysis (Lyell's syndrome) and erythema exsudativum multiforme, rhabdomyolysis, haemolytic anaemia, pancytopenia have been reported.

INFORM DOCTOR ALL UNDESIRABLE EFFECTS

OVERDOSAGE

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 hemodialysis or peritoneal dialysis.

STORAGE

Store below 25°C, protected from light and moisture.

SHELF LIFE : 24 MONTHS.
DO NOT USE OVER EXPIRY DATE.

SUPPLY

LOXOF 250 mg : blister strip of 5 tablets
LOXOF 500 mg : blister strip of 5 tablets

KEEP MEDICINES OUT OF REACH OF CHILDREN.

REFERENCES

1. *Physicians' Desk Reference, 2000, 54th Ed : 1545 - 2165.*
2. *ABPI Compendium of Data Sheets and Summaries of Product Characteristics, 1999 - 2000; 595 - 597.*

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MADE IN INDIA
RANBAXY
LABORATORIES LIMITED
INDUSTRIAL AREA - 2
DEWAS - 455 001

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