1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

PRODUCT NAME: LEOLIN (LEVOFLOXACIN TABLETS 500 MG)

Composition:

Each Film coated tablet contains:

Levofloxacin hemihydrate

Eq. to levofloxacin USP 500mg

Excipients Q.S.

Colour: Approved colour used

Qualitative & Quantitative Formula: **Batch size: 145000 Tablets**

Sr.No	Material Name	Spec	Qty Kg /Batch	Qty mg/ Tablet	Over age	Function
Dry Mixing						
1.	Levofloxacin hemihydrate Eq. to levofloxacin USP	USP	74.284	500	2%	Active Antibacterial
2.	Maize Starch	BP	34.19	235.79	--	Diluent
3.	Lactose	BP	7.100	48.96	--	Diluent
Binder Preparation						
4.	Maize Starch *	BP	5.166	35.58	--	Binder
5.	PVP K 30	BP	0.363	2.503	--	Binder
6.	Purified Water	BP	Q.S	--	--	Vehicle
	Total Weight		**121.103**	**822.833**		
Lubrication						
7.	Purified Talc	BP	1.450	10.00	--	Glidant
8.	Magnesium stearate	BP	1.110	7.650	--	Lubricant
9.	Aerosil 200	BP	0.725	5.00	--	Disintegrant
10.	Sodium Starch Glycolate	BP	2.176	15.00	--	Lubricant
11.	Microcrystalline Cellulose	BP	3.053	21.055	--	Diluent
	Total Weight		**129.617**	**881.538**		
* Note: Actual Quantity of Lactose shall vary as per potency of active Material.						
Film Coating						
12.	Insta-coat (Code No: A05D01455)	--	4. 060	28.00	--	Coating material
13.	Iso Propyl Alcohol	BP	28.45 Liter	--	--	Coating Vehicle
14.	Methylene Dichloride	BP	52.80 liter	--	--	Coating Vehicle

4. Clinical particulars

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

Levofloxacin 500mg Film-coated Tablets is indicated in adults for the treatment of the following infections.

• Acute bacterial sinusitis

• Uncomplicated cystitis

• Acute exacerbation of chronic obstructive pulmonary disease including bronchitis

• Complicated skin and soft tissue infections/complicated skin and skin structure infections for the above-mentioned infections Levofloxacin 500mg Film-coated Tablets should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Acute pyelonephritis and complicated urinary tract infections

• Chronic bacterial prostatitis

• Community-acquired pneumonia

• Inhalation Anthrax: post exposure prophylaxis and curative treatment

Levofloxacin 500mg Film-coated 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.

4.2 Dosage and administration:

Levofloxacin 500mg Film-coated Tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Levofloxacin 500mg Film-coated Tablets may also be used to complete a course of therapy in patients who have shown improvement during initial treatment with intravenous levofloxacin; given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

<u>DOSAGE</u>

Acute Sinusitis: 500 OD for 10-14 days.

Acute exacerbation of chronic bronchitis: 250-500 OD for 7-10 days.

Community acquired Pneumonia: 500 OD/BD for 7-14 days.

Completed UTI: 250 OD for 7-10 days.

Skin and soft tissue infections: 250/500 OD/BD for 7-14 days.

Method of administration

Levofloxacin 500mg Film-coated Tablets tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dose. The tablets may be taken during meals or between meals. Levofloxacin 500mg Film-coated Tablets tablets should be taken at least two hours before or after iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents),and sucralfate administration, since reduction of absorption can occur.

4.3 Contraindications:

Leolin 500 tablets are contraindicated in persons with a history of hypersensitivity to Levofloxacin.

Levofloxacin tablets must not be used:

- In patients hypersensitive to levofloxacin or other quinolones or any of the excipients listed in.
- In patients with epilepsy.
- In patients with history of tendon disorders related to fluoroquinolone administration.
- In children or growing adolescents.
- During pregnancy.
- In breast-feeding women.

4.4 Special Warnings and Precautions for Use

WARNINGS

The safety and efficacy of Levofloxacin in pediatric patients, adolescents (under the age of 18 years), pregnant women, and nursing mother have not been established.

Serious and occasionally fatal hypersensitivity and/or anaphylactic reactions have been reported in patients receiving therapy with Levofloxacin. Levofloxacin should be discontinued immediately at the first appearance of a skin rash or any other sign of hypersensitivity.

PRECAUTION

Levofloxacin should be used with caution in any patient with a known or suspected CNS disorder that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arterioserosis, epilepsy) or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold. Disturbances of blood glucose, including symptomatic hyper- and hypoglycemia, have been reported usually in diabetic patients receiving concomitant treatment of levofloxacin with an oral hypoglycemic agent (e.g., glyburide/glibenamide) or with insulin. In these patients, careful monitoring of blood glucose is recommended.

Tendinitis and tendon rupture

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 fluoroquinolone and have been reported to occur even up to several months after discontinuation of treatment in patients receiving daily doses of 1000 mg levofloxacin. 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.

The daily dose should be adjusted in elderly patients based on creatinine clearance.Close monitoring of these patients is therefore necessary if they are prescribed levofloxacin.

Clostridium difficile-associated disease

Diarrhoea, 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). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider

this diagnosis in patients who develop serious diarrhoea during or after treatment with levofloxacin. 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 predisposed to seizures

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. In case of convulsive seizures treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of haemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose of levofloxacin should be adjusted in patients with renal impairment.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose.Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin. At the time of prescription, patients should be advised of the signs and

symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Prevention of photosensitisation

Photosensitisation has been reported 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), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Patients treated with Vitamin K antagonists

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.

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

QT interval prolongation:

Caution should be taken when using fluoroquinolone, 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 antiarrhythmic, tricyclic antidepressants, macrolides, antipsychotics).
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- 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 fluoroquinolone, including levofloxacin, in these populations.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolone. 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.

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolone, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. Post marketing serious adverse reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

4.5 Interaction with other Medicinal products and other forms of Interaction

Antacids, Sucralfate, Metal Cations, Multivitamins: Concurrent administration of Levofloxacin Tablets with antacids containing magnesium 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.

Theophylline: Theophylline may result in prolonged elimination half-life, elevated serum Theophylline.

Non-steroidal anti-inflammatory drugs: The concomitant administration of a non-steroidal anti-inflammatory drug with a 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 levofloxacin and an antidiabetic agent. Therefore, careful monitoring of blood glucose is recommended when these agents are co administered.

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

Iron salts, zinc-salts, magnesium- or aluminium-containing antacids, didanosine

Levofloxacin absorption is significantly reduced when iron salts, or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) are administered concomitantly with levofloxacin tablets. Concurrent administration of fluoroquinolone with multi-vitamins containing zinc appears to reduce their oral

absorption. It is recommended that preparations containing divalent or trivalent cautions such as iron salts, zinc-salts or magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents should not be taken 2 hours before or after Levofloxacin 500mg Film-coated Tablets administration. Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

The bioavailability of Levofloxacin 500mg Film-coated Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the Levofloxacin 500mg Film-coated Tablets administration.

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

No pharmacokinetic interactions of levofloxacin were found with theophylline 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 were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine (24%) and probenecid (34%). 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.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of levofloxacin on other medicinal products

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 fluoroquinolone, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmic, tricyclic antidepressants, macrolides and, antipsychotics)

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

Other forms of interactions

Food

There is no clinically relevant interaction with food. Levofloxacin 500mg Film-coated Tablets may therefore be administered regardless of food intake.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolone to the weight-bearing cartilage of the growing organism, levofloxacin must not be

used in pregnant women.

Breastfeeding

Levofloxacin 500mg Film-coated Tablets is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolone are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolone to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women.

Fertility

Levofloxacin caused no impairment of fertility or reproductive performance in rats.

4.7 Effects on Ability to Drive and Use Machines:

Some undesirable effects (e.g. dizziness/vertigo, drowsiness, and visual disturbances) may impair the patient's ability to concentrate and react, and therefore may constitute a risk in situations where these abilities are of special importance (e.g. driving a car or operating machinery).

4.8 Undesirable Effects

Some of the adverse reactions reported with the use of levofloxacin are Diarrhea, nausea, vaginitis, flatulence, pruritus, rash; abdominal pain, genital moniliasis, dizziness, dyspepsia, insomnia, taste perversion, vomiting, anorexia, anxiety, constipation, edema, fatigue, headache, increased sweating, leukorrhea, malaise, nervousness, sleep disorders, tremor & urticaria.

Most adverse reactions are mild to moderate; however, sometimes serious adverse effects occur. There is some disagreement in the medical literature regarding whether and to what extent levofloxacin and other fluoroquinolone produce serious adverse effects more frequently than other broad spectrum antibacterial drugs.

In pooled results from 7537 patients exposed to levofloxacin in 29 clinical trials, 4.3% discontinued treatment due to adverse drug reactions. The most common adverse reactions leading to discontinuation were gastrointestinal, including nausea, vomiting, and constipation. Overall, 7% of patients experienced nausea, 6% headache, 5% diarrhea, 4% insomnia, along with other adverse reactions experienced at lower rates.

4.9 Overdose

Signs of levofloxacin overdoses are ataxia, ptosis, decreased locomotors activity, dyspnea, prostration, tremors, and convulsions. In the event of an acute over dosage, the stomach should be emptied. The patient should be observed and appropriate hydration maintained. Levofloxacin is not efficiently removed by hemodialysis or peritoneal dialysis. Overdosing experiments in animals showed central effects such as dizziness, confusion and seizures, as well as prolongation of the QT interval and gastrointestinal disorders.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: quinolone antibacterial, fluoroquinolone, ATC code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

PK/PD relationship

The degree of the bactericidal activity of levofloxacin depends on the ratio of the maximum concentration in serum (Cmax) or the area under the curve (AUC) and the minimal inhibitory concentration (MIC).

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. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolone is observed.

Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/l).
EUCAST clinical MIC breakpoints for levofloxacin.

Pathogen	Susceptible	Resistant
Enterobacteriacae	≤1 mg/l	>2 mg/l
Pseudomonas spp.	≤1 mg/l	>2 mg/l
Acinetobacter spp.	≤1 mg/l	>2 mg/l
Staphylococcus spp.	≤1 mg/l	>2 mg/l
S. pneumonia	≤2 mg/l	>2 mg/l
Streptococcus A,B,C,G	≤1 mg/l	>2 mg/l
H. influenzae	≤1 mg/l	>1 mg/l
M. catarrhalis	≤1 mg/l	>1 mg/l
Non-species related breakpoints	≤1 mg/l	>2 mg/l

1. The breakpoints for levofloxacin relate to high dose therapy

2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with H. influenza

3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary,

expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Aerobic Gram-positive bacteria

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

Aerobic Gram- negative bacteria

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

Anaerobic bacteria

- *Peptostreptococcus*

Other

- *Chlamydophila pneumoniae*
- *Chlamydophila psittaci*
- *Chlamydia trachomatis*
- *Legionella pneumophila*
- *Mycoplasma pneumoniae*

- *Mycoplasma hominis*
- *Ureaplasma urealyticum*

Species for which acquired resistance may be a problem

Aerobic Gram-positive bacteria

- *Enterococcus faecalis*
- *Staphylococcus aureus* methicillin-resistant[#]
- Coagulase negative *Staphylococcus spp*

Aerobic Gram- negative bacteria

- *Acinetobacter baumannii*
- *Citrobacter freundii*
- *Enterobacter erogenes*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Morganella morganii*
- *Proteus mirabilis*
- *Providencia stuartii*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Anaerobic bacteria

- *Bacteroides fragilis*

Inherently Resistant Strains

Aerobic Gram-positive bacteria

- *Enterococcus faecium*

[#] Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolone, including levofloxacin.

5.2 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.

Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

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.

Penetration into tissues and body fluids:

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

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for <5% of the dose and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination

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

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.

Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photo mutagenicity assay, and it reduced tumors development in a photocarcinogenity study.

In common with other fluoroquinolone, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Maize Starch	BP
Lactose	BP
PVP K 30	BP
Purified Water	BP
Purified Talc	BP
Magnesium stearate	BP
Aerosil 200	BP
Sodium Starch Glycolate	BP
Microcrystalline Cellulose	BP
Insta-coat (Code No: A05D01455)	--
Iso Propyl Alcohol	BP
Methylene Dichloride	BP

6.2 Shelf Life

36 Months

6.3 Special Precautions for Storage

Store at temperature below 30°C in a dry place. Protect from light. Keep out of the reach of children.

6.4 Nature and Contents of Container

1 x 7 Alu-Alu TABLETS
2 X 7 Alu-Alu TABLETS

6.5 Special Precautions for Disposal and Other Handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

None

8. MARKETING AUTHORISATION NUMBER(S)

None

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable