SUMMARY OF PRODUCT CHARACTERSTICS

1. NAME OF THE MEDICINAL PRODUCT

1.1 (Invented) name of the medicinal product

Levotama-500

1.2 Strength

Levofloxacin-500 mg

1.3 Pharmaceutical form

Tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Quantitative Composition Quantitative Composition

Sr. No.	Name of Ingredients	Sp.	Label Claim	Over-ages %	Std. Qty. In Kgs	Batch Qty. In Kgs	Std. Qty. per tablet (mg)
DRY MIX							
1	Levofloxacin Hemihydrate eq. to Levofloxacin*	USP	500 mg		51.300	51.300	513.00
2	Maize Starch	BP			9.618	9.618	96.18
3	Micro crystalline cellulose	BP			4.550	4.550	45.50
4	Colloidal Silicon Dioxide	BP			0.344	0.344	3.44
5	Cross Carmellose Sodium	BP			0.500	0.500	5.00
BINDER PREPRATION							
6	Maize Starch (Paste)	BP			3.000	3.000	30.00
7	Methyl Paraben Sodium	BP			0.040	0.040	0.40
8	Propyl Paraben Sodium	BP			0.008	0.008	0.08
9	Purified Water	BP			24.000	24.000	240.00
LUBRICATION							
10	Purified Talc	BP			2.000	2.000	20.00
11	Magnesium Stearate	BP			1.400	1.400	14.00
12	Colloidal silicon dioxide	BP			0.320	0.320	3.20
13	Sodium Starch Glycollate	BP			1.400	1.400	14.00
14	Cross Carmellose Sodium	BP			0.520	0.520	5.20
15	Maize Starch (Dried) **	BP			1.262		12.61

* Levofloxacin to be calculated on assay basis & the quantity to be compensated with maize Starch dried **.

Film Coating Material

Sr. No.	Name of Ingredients	Sp.	Std. Qty. In Kgs	Batch Qty. In Kgs	Std. Qty. per tablet (mg)
1	Titanium Dioxide	BP	0.254	0.254	2.54
2	Red Oxide of Iron	IHS	0.120	0.120	1.20
3	P.V.P.K-30	BP	0.150	0.150	1.50
4	HPMC	BP	1.125	1.125	11.25
5	Purified Talc	BP	0.150	0.150	1.50
6	PEG-6000	BP	0.350	0.350	3.50
8	Purified Water	BP	10.000	10.000	---

Abbreviations

BP **:** British Pharmacopoeia (Current edition)
USP **:** United State Pharmacopoeia (Current edition)
IHS **:** In house Specification

3. PHARMACEUTICAL FORM

Tablet

Description
Reddish Brown coloured, elongated shape ,biconvex film coated tablet having central break line on one side and Plain on other side.

4. CLINICAL PARTICULARS

Levofloxacin 500mg Film-coated Tablets is indicated in adults for the treatment of the following infections:
• Acute bacterial sinusitis
• Acute exacerbations of chronic bronchitis
• Community-acquired pneumonia
• Complicated skin and soft tissue infections

For the above-mentioned infections Levofloxacin 500mg Film-coated 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.
• Pyelonephritis and complicated urinary tract infections)
• Chronic bacterial prostatitis
• Uncomplicated cystitis)
• 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 Posology and Method of Administration:

Levofloxacin tablets are administered once or twice daily. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.
Levofloxacin 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.

Posology

The following dose recommendations can be given for Levofloxacin:
Dosage in patients with normal renal function (creatinine clearance > 50ml / min)

Indication	**Daily dose regimen (according to severity)**	**Duration of treatment**
Acute bacterial sinusitis	500 mg once daily	10 -14 days
Acute bacterial exacerbations of chronic bronchitis	500 mg once daily	7 – 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 – 14 days
Pyelonephritis	500 mg once daily	7-10 days
Uncomplicated cystitis	250 mg once daily	3 days

Complicated urinary tract infections	500 mg once daily	7 – 14 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500mg once or twice daily	7 – 14 days
Inhalation Anthrax	500 mg once daily	8 weeks

Special populations

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

	Dose regimen		
	250 mg / 24 h	**500 mg / 24 h**	**500 mg /12 h**
Creatinine clearance	*first dose: 250 mg*	*first* dose : 500 mg	*first* dose : 500 mg
50-20 ml / min	*then* : 125 mg / 24 h	*then :* 250 mg / 24 h	*then :* 250 mg / 12 h
19 – 10 ml / min	*then* : 125 mg / 48 h	*then :* 125 mg / 24 h	*then :* 125 mg / 12 h
< 10 ml / min (including haemodialysis and 1 CAPD	*then* : 125 mg / 48 h	*then :* 125 mg / 24 h	*then :* 125 mg / 24 h

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 metabolised 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. (also see section 4.4 regarding QT interval prolongation).

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents (less than 18 years of age).

Method of administration

Levofloxacin tablets should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals. Levofloxacin 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

Levofloxacin Tablets must not be used:
- in patients hypersensitive to levofloxacin or other quinolones
- 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 special Precautions for use

Methicillin-resistant Staphylococcus aureus (MRSA)

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 (and commonly recommended antibacterial agents for the treatment of MRSA-infections are considered inappropriate).

Levofloxacin may be used in the treatment of Acute Bacterial Sinusitis and Acute Exacerbation of Chronic Bronchitis when these infections have been adequately diagnosed.
Resistance to fluoroquinolones of E. coli – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in E. coli to fluoroquinolones.
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.

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, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. 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. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with Levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

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 Tablets should be stopped immediately and appropriate treatment initiated without delay (e.g. oral metronidazole or vancomycin). Medicinal products inhibiting the peristalsis 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 Tablets should be adjusted in patients with renal impairment. .

Hypersensitivity reactions
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema 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 bullous reactions
Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin . Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.
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 a history of psychiatric disease.

QT interval prolongation

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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
- uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- 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.

Peripheral neuropathy

Sensory or sensorimotor peripheral neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset . Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an 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 . 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

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

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin

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 fluoroquinolones with multi-vitamins containing zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations 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 Tablets administration . Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate
The bioavailability of Levofloxacin Tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levofloxacin Tablets, it is best to administer sucralfate 2 hours after the Levofloxacin tablet 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 effect 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 the 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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotic).

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

Meals
There is no clinically relevant interaction with food. Levofloxacin Tablets may therefore be administered regardless of food intake.

4.6 Pregnancy and lactation

Pregnancy

There are limited amount of data with respect to 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 fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women

Breast-feeding
Levofloxacin tablets are contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however other fluoroquinolones are excreted in breast milk. In the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones 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, 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

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.
Frequencies are defined using the following convention: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1,000, < 1/100), rare (≥ 1/10,000, < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Not known (cannot be estimated from available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance		
Blood and lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropeniad	Pancytopenia Agranulocytosis Haemolytic anaemia
Immune system disorders			Angioedema Hypersensitivity	Anaphylactic shock[a] Anaphylactoid shock [a]
Metabolism and nutrition disorders		Anorexia	Hypoglycaemia particularly in diabetic patients	Hyperglycaemia Hypoglycaemic coma
Psychiatric disorders	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with e.g. hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt
Nervous system disorders	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion Paraesthesia	Peripheral sensory neuropathy Peripheral sensory motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder

				Ageusia Syncope Benign intracranial hypertension
Eye disorders			Visual disturbances such as blurred vision	Transient vision loss
Ear and Labyrinth disorders		Vertigo	Tinnitus	Hearing loss Hearing impaired
Cardiac disorders			Tachycardia, Palpitation	Ventricular tachycardia, which may result in cardiac arrest Ventricular arrhythmia and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnoea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis Pancreatitis
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)	Blood bilirubin increased		Jaundice and severe liver injury, including cases with fatal acute liver failure, primarily in patients with severe underlying diseases Hepatitis
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction

				Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g. Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) Ligament rupture Muscle rupture Arthritis
Renal and Urinary disorders		Blood creatinine increased	Renal failure acute (e.g. due to interstitial nephritis)	
General disorders and administration site conditions		Asthenia	Pyrexia	Pain (including pain in back, chest, and extremities)

[a] Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose
[b] Mucocutaneous reactions may sometimes occur even after the first dose
Other undesirable effects which have been associated with fluoroquinolone administration include:
• attacks of porphyria in patients with porphyria.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin tablets are central nervous symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.
CNS effects include confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation. Antacids may be used for protection of gastric mucosa. Haemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body.
No specific antidote exists.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Quinolone antibacterials-Fluroquinolone
ATC code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S(-) enatiomer of the racemic drug 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 (C_{max}) 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 *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to levofloxacin.

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

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 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 100 l after single and repeated 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 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 ($t_{½}$: 6 – 8 h). 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.

Special populations

Subjects 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:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl_{cr} [ml/min]	<20	20 – 49	50 – 80
Cl_R [ml/min]	13	26	57
$t_{½}$ [h]	35	27	9

Elderly subjects

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

Gender differences

Separate analysis for male and female subjects showed a small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard 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 foetuses 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 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 photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity study.

In common with other fluoroquinolones, 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
- Micro crystalline cellulose
- Colloidal Silicon Dioxide
- Cross Carmellose Sodium
- Maize Starch (Paste)

- Methyl Paraben Sodium
- Propyl Paraben Sodium
- Purified Water
- Maize Starch (Dried)
- Purified Talc
- Magnesium Stearate
- Colloidal silicon dioxide
- Sodium Starch Glycollate
- Cross carmellose sodium

6.2 Incompatibilities
None

6.3 Shelf life
36 months from the date of manufacturers

6.4 Special precautions for storage
Do not store above 30°C.

6.5 Nature and contents of container

1 x 10's Alu alu blister packed in a unit carton; such cartons are packed in a corrugated box.

6.6 Special precautions for disposal

Tablets should be handled with care.
Do not crush or chew tablets.

7. REGISTRANT

Name of Registrant:
Maxtar Bio-Genics

Address of Office:
310, Pearls Corporate (W Mall),
Manglam Place ,Sector- 3,Rohini,
Delhi-85 India.

8. MANUFACTURER
Name of Manufacturer:
Maxtar Bio-Genics

Address of Manufacturer:
K. No. 705, Nalagarh road, Malku Majra,

(Baddi), Tehsil Nalagarh ,Distt. Solan,
Himachal Pradesh - 173205
INDIA

9. DATE OF REVESION OF THE TEXT
Fresh Authorization