SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE MEDICINAL PRODUCT

LEXOVIN TABLET

(Levofloxacin Tablets 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Sr. No.	Ingredients	Specification	Qty/ Tab mg	Ovg.
1.	Levofloxacin Hemihydrate Equivalent to Levofloxacin	IH	512.000 □ 500.000	--
2.	Microcrystalline cellulose	BP	81.000	--
3.	Povidone (K – 30)	BP	9.000	--
4.	Crospovidone	BP	27.000	--
5.	Colloidal anhydrous silica	BP	6.000	--
6.	Magnesium stearate	BP	5.000	--
7.	Sodium lauryl sulphate	BP	10.000	--
8.	Hypromellose (E – 15)	BP	10.700	--
9.	Isopropyl alcohol	BP	45.000	--
10.	Titanium dioxide	BP	3.000	–
11.	Macrogols - 6000	BP	1.000	--
12.	Propylene glycol	BP	1.000	--
13.	Purified talc	BP	1.300	--
		TOTAL	667.000	

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

For the treatment of the following infections:

i) Acute bacterial sinusitis

ii) Acute exacerbations of chronic bronchitis

iii) Community-acquired pneumonia

iv) Complicated skin and soft tissue infections

v) Complicated urinary tract infections

vi) Chronic bacterial prostatitis

vii) Uncomplicated cystitis

viii) Inhalation anthrax

4.2 Posology and Method of Administration

Route of administration: Oral

The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen.

i) Acute bacterial sinusitis:

500 mg once daily, 10 to 14 days

ii) Acute bacterial exacerbations of chronic bronchitis : 500 mg once daily, 7 to 10 days

iii) Community acquired pneumonia :

500 mg once or twice daily, 7 to 14 days

iv) Pyelonephritis :

500 mg once daily, 7 to 10 days

v) Complicated urinary tract infections :

500 mg once daily, 7 to 14 days

vi) Uncomplicated cystitis :

250 mg once daily, 3 days

vii) Chronic bacterial prostatitis :

500 mg once daily, 28 days

viii) Complicated skin and soft tissue infections :

500 mg once or twice daily, 7 to 14 days

ix) Inhalation anthrax :

500 mg once daily, 8 weeks

x) Impaired liver function :

No adjustment of dose is required since Levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.

xi) Elderly population:

No adjustment of dose is required in the elderly population.

xii) Paediatric population:

It is contraindicated in children and growing adolescents.

4.3 Contraindications

Levofloxacin tablets must not be used:

In patients hypersensitive to Levofloxacin or other quinolones or any of the excipients

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

i) Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with Levofloxacin may be symptomatic of Clostridium difficile - associated disease (CDAD). Levofloxacin should be stopped immediately and appropriate treatment initiated without delay.

ii) It 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.

iii) Since Levofloxacin is excreted mainly by the kidneys, the dose should be adjusted in patients with renal impairment.

iv) Levofloxacin can cause serious, potentially fatal hypersensitivity reactions. Patients should discontinue treatment immediately and contact their physician.

v) Photosensitization has been reported with Levofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitization.

vi) Due to possible increase in 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.

vii) Caution is recommended if Levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

viii) Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

ix) Levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. So, Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

4.5 Interaction with other medicinal products and other forms of interaction

A) Effect of other medicinal products

i) **Iron salts, zinc salts, magnesium- or aluminium-containing antacids, didanosine**

Levofloxacin absorption is significantly reduced when iron salts, or magnesium - or aluminium-containing antacids, are administered concomitantly.

Concurrent administration with multi-vitamins containing zinc appears to reduce their oral absorption.

Calcium salts have a minimal effect on the oral absorption of Levofloxacin.

ii) **Sucralfate**

The bioavailability is significantly reduced when administered together with sucralfate.

iii) **Theophylline, non-steroidal anti-inflammatory drugs**

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.

iv) **Probenecid and Cimetidine**

Probenecid and Cimetidine had a statistically significant effect on the elimination of Levofloxacin.

Caution should be exercised when Levofloxacin is co administered with drugs that affect the tubular renal secretion such as Probenecid and Cimetidine, especially in renally impaired patients.

B) Effect on other medicinal products

ι) **Cyclosporine**

The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

ιι) **Vitamin K antagonists**

Increased coagulation tests 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.

ιιι) **Drugs known to prolong QT interval**

Levofloxacin 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, and antipsychotics)

4.6 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 fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin must not be used in pregnant women.

Breast-feeding

It is 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, 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

- Tendon Effects
- Exacerbation of Myasthenia Gravis
- Hypersensitivity Reactions
- Other Serious and Sometimes Fatal Reactions
- Hepatotoxicity
- Central Nervous System Effects
- Clostridium difficile-Associated Diarrhea
- Peripheral Neuropathy
- Prolongation of the QT Interval
- Musculoskeletal Disorders in Pediatric Patients
- Blood Glucose Disturbances
- Photosensitivity/ Phototoxicity
- Development of Drug Resistant Bacteria
- Crystalluria and cylindruria have been reported with quinolones, including levofloxacin. Therefore, adequate hydration of patients receiving Levofloxacin should be maintained to prevent the formation of highly concentrated urine.

4.9 Overdose

Symptoms of Overdosage:

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, central nervous system 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.

Treatment:

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.

5.1 Pharmacodynamic Properties

Therapeutic category: Quinolone antibacterial, fluoroquinolones

Mechanism of action

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

ιι) Levofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. This can also affect mammalian cell replication.

ιιι) In particular, some congeners of this drug family display activity not only against bacterial topoisomerases but also against eukaryotic topoisomerases, and are toxic to cultured mammalian cells and *in vivo* tumor models.

5.2 Pharmacokinetic Properties

A. **Absorption**

i) 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 %.

ii) Food has little effect on the absorption of Levofloxacin.

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

B. **Distribution**

ι) Approximately 30 - 40 % of Levofloxacin is bound to serum protein.

ιι) The mean volume of distribution of Levofloxacin is approximately 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

ιιι) 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 into cerebro-spinal fluid.

C. **Biotransformation**

i) Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide.

ii) These metabolites account for < 5 % of the dose and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

D. **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.

5.3 Preclinical Safety Data

ι) 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.

ιι) 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.

ιιι) 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.

ιϖ) 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 photocarcinogenity study.

ϖ) 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

1.	Microcrystalline cellulose	BP
2.	Povidone (K – 30)	BP
3.	Crospovidone	BP

4.	Colloidal anhydrous silica	BP
5.	Magnesium stearate	BP
6.	Sodium lauryl sulphate	BP
7.	Hypromellose (E – 15)	BP
8.	Isopropyl alcohol	BP
9.	Titanium dioxide	BP
10.	Propylene glycol	BP
11.	Purified talc	BP
12.	Macrogols – 6000	BP

6.2 Incompatibilities

None

6.3 Shelf Life

Three years

6.4 Special Precautions for Storage

Store at temperature not exceeding 30°C

6.5 Nature and contents of container

Alu-Alu Blister Pack of 10 Tablets

6.6 Special precautions for disposal and other handling

No special requirement

7. Applicant/Manufacturer

MANUFACTURER BY:

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