1.3 Product information

1.3.1 Summary of Product Characteristics (SmPC)

1. Name of the medicinal Product

1.1 Product name:
LEVOFLOXACIN TABLETS USP 500 MG

1.2 Strength:
Each film coated tablet contains:
Levofloxacin Hemihydrate USP
Eq. to Levofloxacin 500mg
Excipients Q.S
Colour: Red oxide of Iron & Titanium Dioxide BP

1.3 Pharmaceutical dosage forms: Oral-Film Coated Tablet

2. Qualitative and Quantitative composition:

Sr. No.	Ingredients	Label Claim (mg)	Req. Qty/ Tablet (mg)	Overages %	Actual Qty/Tablet (mg)	Actual Qty/batch (kg)	Function
Dry Mixing							
1.	Levofloxacin Hemihydrate USP Eq. to Levofloxacin*	500.0	512.470	-	512.470	51.247	Antibacterial
2.	Microcrystalline cellulose phosphate BP	-	14.030	-	14.030	1.403	Diluent
3.	Maize Starch BP	-	6.500	-	6.500	0.650	Diluent
Binding							
4.	Povidone BP	-	5.000	-	5.000	0.500	Binder
5.	Purified Water BP**	-	0.120 ml	-	0.120 ml	12.000 Ltr	Vehicle
Blending & Lubrication							
6.	Purified Talc BP	-	8.000	-	8.000	0.800	Glidant
7.	Magnesium Stearate BP	-	16.000	-	16.000	1.600	Lubricant
8.	Sodium Starch glycolate BP	-	8.500	-	8.500	0.850	Disintegrant
9.	Colloidal Anhydrous Silica BP	-	4.500	-	4.500	0.450	Glidant
10.	Croscarmellose Sodium BP	-	10.000	-	10.000	1.000	Disintegrant

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Total Weight of Uncoated Tablet					**585.00mg**	**58.50kg**	
Coating							
11.	Colorezy White 17F580001 IH ***	-	17.550	-	17.550	1.755	Film Former
12.	Lake of Red oxide of Iron IH	-	0.700	-	0.700	0.070	Colorant
13.	Purified Water BP**	-	0.0878 ml	-	0.0878 ml	8.780 Ltr	Solvent
Total Weight of Film Coated Tablet					**603.25mg**	**60.325 kg**	

*Calculation of Levofloxacin Hemihydrate USP Eq. to Levofloxacin 500 mg

$$= \frac{500 \times 370.38}{361.37}$$

= 512.47 mg

Amount of Levofloxacin Hemihydrate is adjusted on the basis of assay and water content

** Material will not remain in final product

***Composition of Colorezy white 17F580001:**

Components	**Quantity per kg**
HPMC 6 CPS BP	625 gm
Purified Talc BP	150 gm
PEG 6000 BP	125 gm
Titanium Dioxide BP	100 gm

3. Pharmaceutical forms

Oral-Film Coated Tablet

4. Clinical Particulars

4.1 Therapeutic Indications

Levofloxacin Tablets is indicated in adults for the treatment of the following infections;

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Uncomplicated urinary tract infections
- Complicated urinary tract infections (including pyelonephritis)
- Chronic bacterial prostatitis
- Skin and soft tissue infections

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4.2 Posology and Method of administration

Adult:

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.

Dosage in patients with normal renal function

(Creatinine clearance > 50 ml/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
Complicated urinary tract infections	500 mg once daily	7 - 14 days
Uncomplicated cystitis	250 mg once daily	3 days
Chronic bacterial prostatitis	500 mg once daily	28 days
Complicated Skin and soft tissue infections	500 mg once or twice daily	7 - 14 days
Inhalation Anthrax	500 mg once daily	8 weeks

Impaired hepatic 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.

In the elderly

No adjustment of dosage is required in the elderly, other than that imposed by consideration of renal function.

In children

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

Method of administration

For oral use

Irbesartan should be taken once daily with or without food.

4.3 Contraindications

The use of Levofloxacin is contra-indicated in:

- 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 (up to age of 18)

- During pregnancy
- In breast-feeding women

4.4 Special warning and precaution for use

- Risk of tendinitis and tendon rupture is increased. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroids, and in patients with kidney, heart or lung transplants. Discontinue if pain or inflammation in a tendon occurs.
- It may exacerbate muscle weakness in persons with myasthenia gravis. Avoid use in patients with a known history of myasthenia gravis.
- Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose.
- Hematologic (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses.
- Hepatotoxicity: Severe, and sometimes fatal, hepatoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur.
- Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold. Increased intracranial pressure (pseudotumor cerebri) has been reported.
- Clostridium difficile associated colitis: evaluate if diarrhea occurs.

4.5 Interaction with other medicinal products and other forms of interactions

Effect of other medicinal products on levofloxacin:

Iron salts, magnesium- or aluminium-containing antacids

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

Sucralfate

The bioavailability of Levofloxacin tablets is significantly reduced when administered together with sucralfate.

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.

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%).

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).

Drugs known to prolong 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, antipsychotics).

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 Fertility, pregnancy and lactation

Pregnancy

There are limited amount of data with respect to the use of levofloxacin in pregnant women.

Breast-feeding

evofloxacin tablets are contraindicated 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

Not known

4.8 Undesirable effects

Most common side effects associated with Levofloxacin are as follow:

Tachycardia, Leukopoenia, eosinophilia, Thrombocytopenia, neutropenia, Agranulocytosis, Pancytopenia, haemolytic anaemia, Dizziness, headache, somnolence, Convulsion, tremor, paraesthesia, Visual disturbances, Vertigo, Hearing impaired, Tinnitus, Bronchspasm, dyspnoea, Pneumonitis allergic, Diarrhoea, nausea, Vomiting, abdominal pain, dyspepsia, flatulence, constipation, Blood creatinine increased, Renal failure acute, Rash, pruritis, Urticaria, Angioneurotic oedema, photosensitivity reaction, Rhabdomyolysis, Anorexia, Hypoglycaemia, Fungal infection, Hypotension, Asthenia, Pyrexia, Anaphylactic shock, Hepatic enzyme increased, Blood bilirubin increased, Hepatitis, Insomnia, nervousness, Psychotic disorder, depression, confusional state, agitation, anxiety.

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 overdosage of levofloxacin 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. 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

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

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 100 l after single and repeated 500 mg doses, indicating widespread distribution into body tissues.
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.

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.

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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 photomutagenicity assay, and it reduced tumour development in a photocarcinogenity 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
Microcrystalline cellulose
Povidone K-30
Purified Water
Purified Talc
Magnesium Stearate
Sodium Starch Glycolate
Colloidal Anhydrous Silica
Croscarmellose Sodium
Colorezy White 17F580001
Lake of red oxide of iron
Purified Water

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

36 Months from the date of manufacturing

6.4 Special precautions for storage

Store at a temperature not exceeding 30ºC in a dry place. Protect from light. Keep out of reach of children.

6.5 Nature and contents of container

Primary Packing: Alu/Alu Strips of 10 Tablets packed in Printed Aluminium foil from one side and plain aluminium foil from the other side.

Secondary Packing: Such 1 Strips is packed in printed carton along with package insert.

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6.6 **Special precautions for disposal and other handling**
Not Applicable

7. **Marketing authorisation holder and manufacturing site addresses**
STALLION LABORATORIES PVT. LTD.
C-1B, 305/2, 3, 4 & 5, G.I.D.C, KERALA (BAVLA),
DIST.: AHMEDABAD,
GUJARAT, INDIA.

8. **Marketing authorisation numbers**
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9. **Date of First Registration/Renewal of the Registration**
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10. **Date of revision of Text**
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11. **Dosimetry (If Applicable)**
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12. **Instructions for Preparation of Radiopharmaceuticals (If Applicable)**

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