SUMMARY PRODUCT CHARACTERISTICS (SPC)

1. Name of the medicinal product

AARLEFLOX 500 (Levofloxacin Tablets USP)

2. Quality and Quantitative Composition

Each Film Coated Tablet contains:
Levoflxoacin (Hemihydrate) USP
Equivalent to Levofloxacin .....500 mg

For full list of excipients, see section 6.1

3. Pharmaceutical Form

Film Coated Tablet

Brown, caplet shape, biconvex, film coated tablets with break line.

4. Clinical Particulars

4.1 Therapeutic indication

Levofloxacin is licensed for the treatment of acute sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia, but it should only be considered for these infections when first-line treatment cannot be used or is ineffective. Levofloxacin is also licensed for the treatment of urinary-tract infections, skin and soft-tissue infections, Chronic prostatitis, Inhalation anthrax (treatment and post-exposure prophylaxis).

4.2 Posology and method administration

By mouth, acute sinusitis, 500 mg once daily for 10–14 Days Acute exacerbation of chronic bronchitis, 500mg once daily for 7–10 days Community-acquired pneumonia, 500 mg once or twice daily for 7–14 days Urinary-tract infections, 500 mg once daily for 7–14 days (250 mg once daily for 3 days in uncomplicated infection) Chronic prostatitis, 500mg once daily for 28 days Complicated skin and soft tissue infections, 500mg once or twice daily for 7–14 days Inhalation anthrax (treatment and post-exposure prophylaxis), 500mg once daily for 8 weeks.

4.3 Contraindication

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 Warning and precautions for use

Quinolones should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency, myasthenia gravis (risk of exacerbation), and in children or adolescents (arthropathy has developed in weight-bearing joints in young animals). Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). Quinolones can prolong the QT interval. The CSM has warned that quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them,History of psychiatric illness.

Renal impairment

Usual initial dose then use half normal dose if eGFR 20–50 mL/minute/1.73m2; consult product literature if eGFR less than 20 mL/ minute/1.73m2.

4.5 Interaction with other medicinal products and other forms of interactions

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 multivitamins
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 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 antiinflammatory 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

Pegnancy:

Quinolones should be avoided in pregnancy because they have been shown to cause arthropathy in animal studies; safer alternatives are available; however, a single dose of ciprofloxacin may be used for the prevention of a secondary case of meningococcal meningitis.

Lactation:

In the absence of human data and due to the experimental risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, Levofloxacin must not be used in breast feeding women

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

Side-effects of the quinolones include nausea, vomiting, diarrhoea (rarely antibiotic-associated colitis), headache, and dizziness. Less frequent sideeffects include dyspepsia, abdominal pain, anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombocytopenia), arthralgia, myalgia, rash (very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), disturbances in vision and taste. Other side-effects reported rarely or very rarely include hepatic dysfunction (including jaundice and hepatitis), hypotension, vasculitis, dyspnea, convulsions, psychoses, symptoms of peripheral neuropathy (sometimes irreversible), renal failure, interstitial nephritis, tendon inflammation and damage, photosensitivity, disturbances in hearing and smell. The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (including severe rash) occur, also flatulence, constipation, hyperhidrosis; rarely tachycardia, palpitation, abnormal dreams, tinnitus, hypoglycaemia; also reported potentially life-threatening hepatic failure, syncope, benign intracranial hypertension, pneumonitis, peripheral neuropathy, extrapyramidal symptoms, hyperglycaemia, rhabdomyolysis, stomatitis; local reactions and transient hypotension reported with infusion.

Reporting of adverse Effects

Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose and special antidotes

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 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.

5. Pharmacological Properties Clinical Particulars

5.1 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.

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.

Pharmacokinetic properties
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Cl_{CR} [ml/min]	< 20	20 – 49	50 – 80
Cl_R [ml/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

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

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

5.2 Pre clinical 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 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

Corn Starch USP
Microcrystalline cellulose USP
Sodium starch glycolate BP
Purified Talc USP
Colloidal Silicon Dioxide USP
Cross carmellose Sodium USP(NF)
Instacoat Universal Brown (A05D00472) In-House

6.2 Incompatibilities

None

6.3 Shelf Life

24 months

Shelf life after dilution or reconstitution according to directions.
Not applicable

Shelf-life first opening the container.
Not applicable.

6.4 Special precaution for storage

Store below 30^0C. Protect from light.

6.5 Nature and content of container

PVC blister of 10 tablets. 10 such PVC blisters are packed in a printed carton along with the pack Insert.
10 such a printed mono carton in outer printed carton.

7. Marketing Authorization Holder

Pinnacle Life Science Pvt. Ltd.
Mahendra Industrial Estate, Ground Floor
Plot no .109-D, Rd no 29
Sion (East), Mumbai 400 022, INDIA

8. Marketing Authorization Number

H2025/CTD10618/16396

9. Date of first authorization/ renewal of the authorization

20-13-2014

10. Date of the revision of the text

20-13-2014