SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

Levofloxacin 500 mg Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg of levofloxacin (as hemihydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

Brownish red colored, capsule shaped, biconvex film coated tablets debossed ‘T’ & 63 on either side of a deep score line on one side of the tablet and deep score line on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Levofloxacin 500 mg Tablets is indicated in combination with other antituberculosis agents for the treatment of tuberculosis caused by Mycobacterium tuberculosis in adults and adolescents.

Levofloxacin 500 mg Tablets is only indicated as a second-line antimycobacterial drug when use of first line drugs is not appropriate due to resistance or intolerance.

Consideration should be given to official treatment guidelines for tuberculosis, e.g those of WHO: (http://www.who.int/tb/publications/pmdt_companionhandbook/en/).

4.2 Posology and method of administration

Adults and adolescents:
The recommended daily dose is 750 mg for patients weighing 30 kg up to 45.9 kg, and 1000 mg for patients weighing 46 kg or more.

Children
Levofloxacin 500 mg Tablets is not suitable for children. Formulations containing smaller amounts of levofloxacin are available.

Levofloxacin is not recommended for children under 10 kg.

Renal impairment:
For patients with an estimated creatinine clearance < 30 ml/min, with or without haemodialysis, the dose should be reduced to 750-1000 mg/dose given three times per week.

Hepatic impairment:

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority’s (NMRA) responsibility. Throughout this WHOPAR the proprietary name is given as an example only.
No adjustment of dosage is required.

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

**Method of administration**
Levofloxacin 500 mg Tablets should be swallowed whole with a sufficient amount of liquid. The tablets may be taken with or without food. (see also section 4.5).

### 4.3 Contraindications
Levofloxacin 500 mg Tablets is contraindicated:
- in patients with hypersensitivity to levofloxacin, other quinolones or to any of the excipients listed in section 6.1
- in patients with epilepsy
- in patients with history of tendon disorders related to fluoroquinolone administration
- in breast-feeding women

### 4.4 Special warnings and precautions for use

**Tendinitis and tendon rupture**
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. It may occur at any time during therapy and also several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in the elderly, 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 (see section 4.2). 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 (see sections 4.3 and 4.8).

**Clostridium difficile-associated disease**
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin, may be symptomatic of _Clostridium difficile_-associated disease, the most severe form of which is pseudomembranous colitis. If _Clostridium difficile_-associated disease is suspected, levofloxacin must be stopped immediately and appropriate treatment initiated without delay (e.g. oral vancomycin). Products inhibiting peristalsis are contraindicated in this clinical situation.

**Patients predisposed to seizures**
Levofloxacin is contraindicated in patients with a history of epilepsy (see section 4.3) and, as with other quinolones, should be used with caution in patients predisposed to seizures, such as patients with pre-existing central nervous system lesions, concomitant treatment with fenbufen and similar non-steroidal anti-inflammatory drugs, or with drugs which lower the cerebral seizure threshold, such as theophylline (see section 4.5). In case of convulsive seizures, treatment with levofloxacin should be discontinued.
Patients with G-6-phosphate dehydrogenase deficiency
Patients with latent or manifest defects in glucose-6-phosphate dehydrogenase activity may be prone to haemolytic reactions when treated with quinolone antibacterial agents, and so levofloxacin should be used with caution.

Patients with renal impairment
Since levofloxacin is excreted mainly by the kidneys, the dose of Levofloxacin 500 mg Tablets should be adjusted in patients with renal impairment (see section 4.2).

Hypersensitivity reactions
Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately.

Severe bullous reactions
Cases of severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). 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 (see section 4.8).

Prevention of photosensitisation
Although photosensitisation is very rare with levofloxacin, it is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV light (e.g. sunray lamp, solarium), 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 (see section 4.5).

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 (see section 4.8). 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 fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as:
   - 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, methadone).
− uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
− preexisting 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
Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, which can be rapid in its onset. If the patient experiences symptoms of neuropathy, Levofloxacin 500 mg Tablets may be continued only when the benefits are considered to outweigh the risk of irreversible neuropathy.

Patients with myasthenia gravis
Levofloxacin should be used with caution in patients with myasthenia gravis because the symptoms can be exacerbated. Fluoroquinolones, 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.

Hepatobiliary disorders
Cases of hepatic necrosis, including life threatening 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.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

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.

Paediatric population
Due to adverse effects on the cartilage in juvenile animals (see section 5.3), and to limited documentation of the safety and appropriate dose adjustments, levofloxacin should only be used in children and adolescents with M. Tuberculosis infection if the benefit is considered to exceed the risk and there are no treatment alternatives.

4.5 Interaction with other medicinal products and other forms of interaction
Iron 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 500 mg Tablets. Concurrent administration of fluoroquinolones with multi-vitamin preparations with zinc appears to reduce their oral absorption. It is recommended that preparations containing divalent or trivalent cations such as iron salts, zinc salts, magnesium- or aluminium-containing antacids, or didanosine (only didanosine formulations with aluminium or magnesium containing buffering agents) should not be taken within 2 hours before or after administration of Levofloxacin 500 mg Tablets.

Sucralfate

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

Theophylline

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.

NSAIDs

Coadministration with nonsteroidal anti-inflammatory drugs (NSAIDs) may potentiate the risk of central nervous system toxicity sometimes associated with fluoroquinolone use. The interaction has been reported most often with enoxacin. It may occur with other fluoroquinolones as well, but is poorly documented. Patients with a history of seizures may be at greater risk. (see also section 4.4.) 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. Still, 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.

Cyclosporin

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

Vitamin K antagonists

Increases in coagulation parameters (as measured e.g. by 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). Therefore, coagulation parameters should be closely monitored in patients treated with vitamin K antagonists (see section 4.4).

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, methadone). (See section 4.4 “QT interval prolongation”).

**Drugs undergoing renal tubular secretion**

With high doses of quinolones, impairment of excretion and an increase in serum levels may occur when co-administered with other drugs that undergo renal tubular secretion (e.g. probenecid, cimetidine, frusemide and methotrexate).

### 4.6 Fertility, pregnancy and breast-feeding

#### Women of childbearing potential

Pregnancy should be avoided in women treated with levofloxacin. Adequate contraceptive measures should be taken.

**Pregnancy**

There are limited data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However in the absence of human data and due to experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, levofloxacin should only be used in pregnancy if the benefit is considered to outweigh the risks, and there are no available treatment alternatives.

**Lactation**

Levofloxacin 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 experimental data suggesting a risk of damage to the weight-bearing cartilage of the growing organism by fluoroquinolones, Levofloxacin 500 mg Tablets should not be used during breast-feeding (section 5.3).

**Fertility**

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

### 4.7 Effects on ability to drive and use machines

No studies on the effects of levofloxacin on the ability to drive and use machines have been performed. 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

Adverse events considered at least possibly related to levofloxacin treatment are listed below by body system, organ class and frequency. Frequency estimates are in many cases not based on adequately sized randomised trials, but on published data generated during post-approval use. Sometimes, no frequency data can be given. Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1000 to <1/100), rare (≥ 1/10000 to <1/1000), very rare (<1/10000), ‘not known’ (frequency cannot be estimated from the available data). Note that the frequencies relate to short-term therapy (<1 month).
Infections and infestations
Uncommon: fungal infection (and proliferation of other resistant microorganisms of the normal flora)

Blood and lymphatic system disorders
Uncommon: leukopenia, eosinophilia
Rare: thrombocytopenia, neutropenia
Not known: pancytopenia, haemolytic anaemia, agranulocytosis

Immune system disorders
Rare: angioedema hypersensitivity (see section 4.4)
Not known: anaphylactic shock (see section 4.4) anaphylactic and anaphylactoid reactions, which may sometimes occur even after the first dose.

Metabolism and nutrition disorders
Uncommon: anorexia
Rare: hypoglycaemia, particularly in diabetic patients (see section 4.4)
Not known: hyperglycaemia, hypoglycaemic coma (see section 4.4)

Psychiatric disorders
Common: insomnia
Uncommon: anxiety, confusional state, nervousness
Rare: psychotic disorder (with e.g. hallucination, paranoia), depression, agitation, abnormal dreams, nightmares
Not known: psychotic reactions with self-endangering behaviour including suicidal thoughts or acts (see section 4.4)

Nervous system disorders
Common: headache, dizziness
Uncommon: somnolence, tremor, dysgeusia
Rare: convulsion, paraesthesia
Not known: peripheral sensory neuropathy or peripheral sensory motor neuropathy, dyskinesia, extrapyramidal disorders, dysgeusia including ageusia, parosmia including anosmia, syncope, benign intracranial hypertension.

Eye disorders
Rare: visual disturbance
Not known: transient vision loss (see section 4.4)

Ear and Labyrinth disorders
Uncommon: vertigo
Rare: tinnitus
Not known: hearing loss, hearing impaired

Cardiac disorders
Rare: tachycardia, palpitations
Not known: 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 (see sections 4.4 and 4.9).
Vascular disorders
Rare: hypotension

Respiratory, thoracic and mediastinal disorders
Rare: bronchospasm, dyspnoea
Very rare: allergic pneumonitis

Gastrointestinal disorders
Common: diarrhoea, nausea, vomiting
Uncommon: abdominal pain, dyspepsia, flatulence, constipation
Not known: haemorrhagic diarrhoea – which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), pancreatitis

Hepatobiliary disorders
Common: hepatic enzyme increased (ALT/AST, alkaline phosphates, GGT)
Uncommon: blood bilirubin increased
Not known: jaundice and severe liver injury, including cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4), hepatitis

Skin and subcutaneous tissue disorders
Uncommon: rash, pruritus, urticarial, hyperhidrosis
Very rare: angioneurotic oedema,
Not known: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction, leukocytoclastic vasculitis, stomatitis
Mucocutaneous reactions may sometimes occur even after the first dose.

Musculoskeletal and Connective tissue disorders
Uncommon: arthralgia, myalgia
Rare: tendon disorder (see section 4.4) including tendinitis (e.g. Achilles tendon), muscular weakness (which may be of special importance in patients with myasthenia gravis).
Not known: rhabdomyolysis, tendon rupture (see section 4.4) (this undesirable effect may occur within 48 hours of starting treatment and may be bilateral), ligament rupture, muscle rupture, arthritis.

Renal and urinary disorders
Uncommon: blood creatinine increased
Rare: acute renal failure (e.g. due to interstitial nephritis)

General disorders and administration site conditions
Uncommon: asthenia
Rare: pyrexia
Not known: pain (including pain in back, chest, and extremities)

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 supratherapeutic doses, the most important signs to be expected following acute overdosage of Levofloxacin 500 mg Tablets are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval as well as gastrointestinal reactions such as nausea and mucosal erosions.

CNS effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience.

There is no specific antidote. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, fluoroquinolone
ATC code: J01MA12

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

Mechanism of action
Levofloxacin has in vitro activity against M. Tuberculosis, as well as against a wide range of Gram-positive and Gram-negative pathogens. The bactericidal action of levofloxacin against M. Tuberculosis results from the inhibition of the DNA gyrase, encoded by the gyrA and gyrB genes.

The wild-type levofloxacin MIC distribution for clinical isolates of M. Tuberculosis has been reported by different investigators to range between 0.125-0.5 mg/l. When resistance to fluoroquinolones arises, it is generally caused by mutations in gyrA. Cross-resistance within the fluoroquinolone drug class is extensive, though not universal.

Clinical efficacy
Experience of MDR-TB treatment with levofloxacin within clinical trials is limited.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 hour. The absolute bioavailability is approximately 100%. Food has little effect on the absorption of levofloxacin.

No pharmacokinetic data are available for Levofloxacin 500 mg Tablets.

A bioequivalence study was conducted with Levofloxacin 750-mg Tablets, which is proportionally similar to Levofloxacin 500 mg Tablets in composition. Following a single dose of Levofloxacin 750
mg Tablets in healthy volunteers, arithmetic mean (±SD) levofloxacin C\text{max} was 9.16 ± 2.21 µg/ml (8.90) and the mean (±SD) AUC\text{0–inf} was 76.8 ± 10.7 µg•hour/ml (76.0). The reported mean (±SD) t\text{max} for the innovator product is about 1.44±0.73 hours.

**Distribution**
Approximately 30 - 40 % of levofloxacin is bound to serum protein.

**Metabolism**
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 from the plasma with a half-life of 6 - 8 hours. Excretion is primarily by the renal route (> 85 % of the administered dose).

**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:

<table>
<thead>
<tr>
<th>Cl\text{cr} [ml/min]</th>
<th>&lt; 20</th>
<th>20 - 49</th>
<th>50 - 80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl\text{R} [ml/min]</td>
<td>13</td>
<td>26</td>
<td>57</td>
</tr>
<tr>
<td>t\text{1/2} [h]</td>
<td>35</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

No differences in levofloxacin pharmacokinetics have been reported between young and elderly subjects, and between male and female subjects.

**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 photomutagenicity assay, and it reduced tumour development in a photocarcinogenicity study.

As 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

Core tablet: Microcrystalline cellulose, crospovidone, hypromellose, magnesium stearate.

Film coat: hypromellose, titanium dioxide, polyethylene glycol, polysorbate, red iron oxide, yellow iron oxide.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Store below 30°C, in dry place protected from light. Store tablets in the blisters in the provided carton.

6.5 Nature and contents of container

The tablets are provided in orange coloured PVC-Aluminium blister cards of 20 tablets. Each carton contains 5 such blister cards (100 tablets).

The tablets are also provided in orange coloured PVC-Aluminium blister cards of 10 tablets. Each carton contains 9 or 10 such blister cards (90 or 100 tablets).

6.6 Special precautions for disposal

No special requirements.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. SUPPLIER

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24 October 2014

10. DATE OF REVISION OF THE TEXT


References:

General:


Section 4.5


Section 5.1.

Ångeby K et al. J Antimicrob Chemother 2010; 65: 946–952


Gumbo T Antimicrob Agents Chemother 2010;54:1484-1491