

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Refaz 500mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 512.46 mg of levofloxacin hemihydrate equivalent to 500 mg of levofloxacin.

Excipients:

Each tablet contains sunset yellow (E110)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Orange, oblong, biconvex film-coated tablet with a scoreline.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Refaz tablets are indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1)

- Acute bacterial sinusitis
- Acute exacerbations of chronic bronchitis
- Community-acquired pneumonia
- Complicated skin and soft tissue infections.

For the above-mentioned infections Refaz 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 (see section 4.4)
- Chronic bacterial prostatitis.
- Uncomplicated cystitis (see section 4.4)
- Inhalation Anthrax: postexposure prophylaxis and curative treatment (see section 4.4)

Refaz 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

Refaz tablets are administered once or twice daily.

The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Refaz 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 Refaz:

Dosage in patients with normal renal function (creatinine clearance > 50 ml/min)

| Indication | Daily dose regimen (<i>according to severity</i>) | Duration of the treatment (<i>according to severity</i>) |
|-----------------------------------------------------|-----------------------------------------------------|------------------------------------------------------------|
| 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 |

Special populations

Impaired renal function (creatinine clearance \leq 50ml/min)

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

¹ No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

A score line allows adaptation of the dose in patients with impaired renal function.

Impaired liver function

No adjustment of dose 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 dose is required in the elderly, other than that imposed by consideration of renal function (see section 4.4 “Tendinitis and tendon rupture” and “QT interval prolongation”).

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents (see section 4.3).

Method of administration

Refaz tablets should be swallowed without crushing and with sufficient amount of liquid. They may be divided at the score line to adapt the dose. The tablets may be taken during meals or between meals. Refaz 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 (see section 4.5).

4.3 Contraindications

Refaz tablets must not be used:

- in patients hypersensitive to levofloxacin or other quinolones or 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 children or growing adolescents,
- during pregnancy,
- in breast-feeding women.

4.4 Special warnings and precautions for use

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 (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 (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 (see section 4.8). 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 should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products 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 (see section 4.3) 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 (see section 4.5). In case of convulsive seizures (see section 4.8), treatment with levofloxacin should be discontinued.

Patients with glucose-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 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 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 (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 hyperglycaemia and hypoglycaemia 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

Photosensitisation has been reported with levofloxacin (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. sunray lamp or 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 (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, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, 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.

(See section 4.2 Elderly, 4.5, 4.8, 4.9).

Peripheral neuropathy

Peripheral sensory neuropathy and peripheral sensory motor neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. (see section 4.8). 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 (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.

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 (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.

This medicinal product contains the colouring agent sunset yellow (E110), which may cause allergic reactions.

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 Refaz 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 Refaz tablet administration (see section 4.2).

Sucralfate

The bioavailability of Refaz tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and levofloxacin, it is best to administer sucralfate 2 hours after the levofloxacin administration (see section 4.2).

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 affect 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 (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) (see section 4.4 QT interval prolongation).

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*Food*

There is no clinically relevant interaction with food. Refaz tablets may therefore be administered regardless of food intake.

4.6 Fertility, 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 (see section 5.3).

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 (see sections 4.3 and 5.3).

Breast-feeding

The product 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 (see sections 4.3 and 5.3).

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 ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

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 Neutropenia | Pancytopenia Agranulocytosis Haemolytic anaemia |
| Immune system disorders | | | Angioedema Hypersensitivity (see section 4.4) | Anaphylactic shock ^a Anaphylactoid shock ^a (see section 4.4) |
| Metabolism and nutrition | | Anorexia | Hypoglycaemia particularly in | Hyperglycaemia Hypoglycaemic |

| | | | | |
|-----------------------------|----------------------------------------|---------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| disorders | | | diabetic patients (see section 4.4) | coma (see section 4.4) |
| 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 (see section 4.4) |
| Nervous system disorders | Headache Dizziness | Somnolence Tremor Dysgeusia | Convulsion (see sections 4.3 and 4.4) Paraesthesia | Peripheral sensory neuropathy (see section 4.4) Peripheral sensory motor neuropathy (see section 4.4) Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial hypertension |
| Eye disorders | | | Visual disturbances such as blurred vision (see section 4.4) | Transient vision loss (see section 4.4) |
| Ear and Labyrinth disorders | | Vertigo | Tinnitus | Hearing loss Hearing impaired |
| 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) |
| 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 (see sections 4.4 and 4.9) |
| Vascular disorders | Applies to iv form only: Phlebitis | | 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 (see section 4.4) 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 (see section 4.4) Hepatitis |
| 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) |
| Skin and subcutaneous tissue disorders ^b | | Rash Pruritus Urticaria Hyperhidrosis | | Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatitis |
| Musculoskeletal and connective tissue disorders | | Arthralgia Myalgia | Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. | Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) (see |

| | | | | |
|---------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| | | | Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4) | sections 4.3 and 4.4) 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 | Applies to iv form only: Infusion site reaction (pain, reddening) | 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.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via 'freepost'. Alternatively, the traditional post-paid 'yellow card' option may also continue to be used.

FREEPOST

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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 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.

CNS effects including 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 – Fluoroquinolones
ATC code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic active 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 in *Pseudomonas aeruginosa*) and efflux mechanisms may also 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.

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Breakpoints

The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).

EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

| Pathogen | Susceptible | Resistant |
|----------------------------------------------|-------------|-----------|
| Entercobacteriaceae | ≤1 mg/L | >2 mg/L |
| <i>Pseudomonas</i> spp. | ≤1 mg/L | >2 mg/L |
| <i>Acinetobacter</i> spp. | ≤1 mg/L | >2 mg/L |
| <i>Staphylococcus</i> spp. | ≤1 mg/L | >2 mg/L |
| <i>S.pneumoniae</i> ¹ | ≤2 mg/L | >2 mg/L |
| <i>Streptococcus</i> A, B, C, G | ≤1 mg/L | >2 mg/L |
| <i>H. influenzae</i> ^{2, 3} | ≤1 mg/L | >1 mg/L |
| <i>M. catarrhalis</i> ³ | ≤1 mg/l | >1 mg/l |
| Non-species related breakpoints ³ | ≤1 mg/L | >2 mg/L |

1 The breakpoints for levofloxacin relate to high dose therapy.

2 Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.

3 Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant.

4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

COMMONLY SUSCEPTIBLE SPECIES

Aerobic Gram-positive bacteria

Bacillus anthracis
Staphylococcus aureus methicillin susceptible
Staphylococcus saprophyticus
 Streptococci, group C and G
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Aerobic Gram-negative bacteria

Eikenella corrodens
Haemophilus influenzae
Haemophilus para-influenzae
Klebsiella oxytoca
Moraxella catarrhalis
Pasteurella multocida
Proteus vulgaris
Providencia rettgeri

Anaerobic bacteria

Peptostreptococcus

Other

Chlamydophila pneumoniae
Chlamydophila psittaci
Chlamydia trachomatis
Legionella pneumophila
Mycoplasma pneumoniae
Mycoplasma hominis
Ureaplasma urealyticum

SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

Aerobic Gram-positive bacteria

Enterococcus faecalis
Staphylococcus aureus methicillin-resistant
Coagulase negative Staphylococcus spp

Aerobic Gram-negative bacteria

Acinetobacter baumannii
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella pneumoniae
Morganella morganii
Proteus mirabilis
Providencia stuartii
Pseudomonas aeruginosa
Serratia marcescens

Anaerobic bacteria*Bacteroides fragilis***INHERENTLY RESISTANT STRAINS****Aerobic Gram-positive bacteria**

Enterococcus faecium

Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin.

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.

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 into 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 and are 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 ($t_{1/2}$: 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 - 40 | 50 - 80 |
| Cl_R [ml/min] | 13 | 26 | 57 |
| $t_{1/2}$ [h] | 35 | 27 | 9 |

Elderly subjects

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.

5.3 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.

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

| | |
|----------------------|----------------------------|
| <i>Tablet core:</i> | Microcrystalline cellulose |
| | Hydroxypropylcellulose |
| | Crospovidone |
| | Magnesium stearate |
| <i>Film coating:</i> | Hypromellose |
| | Indigo Carmine (E132) |
| | Sunset Yellow (E110) |
| | Iron oxide red (E172) |
| | Macrogol 4000 |
| | Titanium dioxide (E171) |

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

Keep the blister in the outer carton in order to protect from light.

This medicinal product does not require any special temperature storage conditions.

6.5 Nature and contents of container

Transparent PVC/PE/PVDC/Aluminium blister in a carton box.
Pack sizes: Packs of 1, 5, 7 or 10 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Pharmathen S.A.
6, Dervenakion str.
153 51 Pallini
Attiki
Greece

8 MARKETING AUTHORISATION NUMBER

PA1368/007/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 5th December 2011

10 DATE OF REVISION OF THE TEXT

November 2013