

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE - MODULE 1	

1.6.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the Medicinal Product:

Levanix Tablets 500 mg

2. Qualitative & Quantitative Composition:

Each film coated tablet contains 512.46 mg of Levofloxacin Hemihydrate equivalent to 500 mg of Levofloxacin.

3. Pharmaceutical Form:

Film Coated Tablets

4. Clinical Particulars:

4.1 Therapeutic indications

Levanix is indicated in adults for the treatment of the following infections:

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

For the above-mentioned infections Levanix 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
- Chronic bacterial prostatitis
- Uncomplicated cystitis
- Inhalation Anthrax: post exposure prophylaxis and curative treatment

Levanix 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

4.2 Posology and method of administration

Levanix 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.

Treatment time

The duration of therapy varies according to the course of the disease (see table below). As with antibiotic therapy in general, administration of Levofloxacin Tablets should be continued for a minimum of 48 to 72 hours after the patient has become afebrile or evidence of bacterial eradication has been obtained.

Posology

The following dose recommendations can be given for Levanix:

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

Indication	Daily dose regimen (according to severity)	Duration of treatment (according to severity)
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 ≤ 50 ml/min)

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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).

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.

Paediatric population

Levanix is contraindicated in children and growing adolescents.

Method of administration

Levanix tablets should be swallowed without crushing and with sufficient amount of liquid. The tablets may be taken during meals or between meals.

Levanix 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

4.3 Contraindications

Levofloxacin 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 warning & precautions for use

Methicillin-resistant *Staphylococcus aureus* (MRSA):

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 human 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

The daily dose should be adjusted in elderly patients based on creatinine clearance. 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.

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. 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 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. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-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 Levanix should be adjusted in patients with renal impairment.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose. 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. 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.

Prevention of Photosensitisation

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

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. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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 antiarrhythmics, 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.

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. 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. 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

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 *Mucobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products & 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 Levanix 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 Levanix tablet administration . Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate

The bioavailability of Levanix tablets is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and Levanix, it is best to administer sucralfate 2 hours after the Levanix tablet administration.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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 Levanix 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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 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. Levanix tablets may therefore be administered regardless of food intake.

4.6 Pregnancy & lactation

Pregnancy

There are limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. However in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women.

Breast-feeding

Levanix is contraindicated in breast-feeding women. There is insufficient information on the excretion of levofloxacin in human milk; however, other fluoroquinolones are excreted in breast milk.

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

Fertility

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

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

4.7 Effects on ability to drive & 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 ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10000$, $< 1/1000$), very rare ($< 1/10000$), not known (cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations

Uncommon: Fungal infection including candida infection, Pathogen resistance

Blood and lymphatic system disorders

Uncommon: Leukopenia, Eosinophilia

Rare: Thrombocytopenia, Neutropenia.

Not Known: Pancytopenia, Agranulocytosis, Haemolytic anaemia

Immune system disorders

Rare: Angioedema, Hypersensitivity

Not Known: Anaphylactic shock^a, anaphylactoid shock^a.

^a Anaphylactic and anaphylactoid reactions may sometimes occur even after the first dose

Metabolism and nutrition disorders

Uncommon: Anorexia

Rare: Hypoglycemia particularly in diabetic patients

Not Known: Hyperglycaemia, Hypoglycaemic coma

Psychiatric disorders

Common: Insomnia

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

Uncommon: Anxiety, Confusional state, Nervousness

Rare: Psychotic reactions (with e.g. hallucination, paranoia), Depression, Agitation, Abnormal Dreams, Nightmares

Not Known: Psychotic disorders with self-endangering behaviour including suicidal ideation or suicide attempt

Nervous system disorders

Common: Headache, Dizziness

Uncommon: Somnolence, Tremor, Dysgeusia

Rare: Convulsion, Paraesthesia

Not Known: Peripheral sensory neuropathy, Peripheral sensory motor neuropathy, Parosmia including anosmia, Dyskinesia, Extrapyrarnidal disorder, Ageusia, Syncope, Benign intracranial hypertension

Eye disorders

Rare: Visual disturbance such as blurred vision

Not Known: Transient vision loss

Ear and Labyrinth disorders

Uncommon: Vertigo

Rare: Tinnitus

Not known: Hearing loss, hearing impaired

Cardiac disorders

Rare: Tachycardia, Palpitation

Not Known: Ventricular tachycardia, which may result in cardiac arrest, Ventricular arrhythmias and torsade de pointes (reported predominantly in patients with risk factors of QT prolongation), electrocardiogram QT prolonged

Vascular disorders

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

Not Known: Bronchospasm, Pneumonitis allergic

Gastrointestinal disorders

Common: Diarrhea, Vomiting, Nausea

Uncommon: Abdominal pain, Dyspepsia, Flatulence, Constipation

Not Known: Diarrhea–hemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, Pancreatitis

Hepatobiliary disorders

Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)

Uncommon: Blood bilirubin increased

Not known: Jaundice and severe liver injury, including cases with acute liver failure, have been reported with Levofloxacin, primarily in patients with severe underlying diseases, Hepatitis

Skin and subcutaneous tissue disorders^b

Uncommon: Rash, Pruritus, Urticaria, Hyperhidrosis

Not Known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, photosensitivity reaction, Leukocytoclastic vasculitis, Stomatitis

^b Mucocutaneous reactions may sometimes occur even after the first dose

Musculoskeletal and Connective tissue disorders

Uncommon: Arthralgia, Myalgia

Rare: Tendon disorder including tendinitis (e.g. Achilles tendon), Muscular weakness which may be of importance in patients with myasthenia gravis.

Not Known: Rhabdomyolysis, Tendon rupture, Ligament rupture, Muscle rupture, Arthritis

Renal and urinary disorders

Uncommon: Blood creatinine increased

Rare: Renal failure acute (e.g. due to interstitial nephritis)

General disorders and administration site conditions

Uncommon: Asthenia

Rare: Pyrexia

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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 supra-therapeutic doses, the most important signs to be expected following acute overdose of Levanix 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

5.0 Pharmacological Properties

5.1 Pharmacodynamics

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).

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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.

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
Enterobacteriaceae	≤1 mg/l	>2 mg/l
<i>Pseudomonas spp.</i>	≤1 mg/l	>2 mg/l
<i>Acinetobacter spp.</i>	≤1 mg/l	>2 mg/l
<i>Staphylococcus spp.</i>	≤1 mg/l	>2 mg/l
<i>S. pneumoniae</i> ¹	≤2 mg/l	>2 mg/l
<i>Streptococcus A,B,C,G</i>	≤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 ⁴	≤1 mg/l	>2 mg/l

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

1. The breakpoints for levofloxacin relate to high dose therapy.
2. Low-level fluoroquinolone resistance (ciprofloxacin MIC's 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

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE - MODULE 1	

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 Pharmacokinetics

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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

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:

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE – MODULE 1	

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl _{cr} [ml/min]	< 20	20 - 49	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 photocarcinogeny 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.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE - MODULE 1	

6. Pharmaceutical Particulars:

6.1. List of excipients:

S. NO.	MATERIAL	QUANTITY	FUNCTION
CORE EXCIPIENTS			
1.	Microcrystalline Cellulose BP (Grade 101)	90.00	Diluent
2.	Maize Starch Ph.Eur.	84.54	Diluent/Binder
3.	Crospovidone (Type A) BP	28.000	Disintegrant
4.	Sodium Stearyl Fumarate USP	10.000	Lubricant
5.	Purified Water USP/BP	Q.s.	Granulating agent
COATING EXCIPIENTS			
1.	Titanium Dioxide BP	1.900	Opacifier
2.	Hypromellose BP/Ph.Eur. (E6 LV)	10.880	Coating agent
3.	Macrogol 6000 BP	2.000	Plasticizer
4.	Ferric Oxide Yellow USPNF	0.200	Colorant
5.	Ferric Oxide Red USPNF	0.020	Colorant
6.	Purified Water USP/BP	Q.s.	Solvent

6.2. Incompatibilities:

None known

6.3. Shelf life:

36 months

6.4. Special precautions for storage:

Store below 30°C

6.5. Nature & contents of container:

The tablets are packed in Alu/Alu blisters and placed in a printed carton along with a pack insert.

Pack size: 7's.

PRODUCT	LEVANIX TABLETS 500 mg
REGISTRATION FILE - MODULE 1	

6.6 Manufacturer:

Neopharma, Abu Dhabi, UAE
Plot No. A1 89-95,
Industrial City of Abu Dhabi (ICAD),
Mussafah, Abu Dhabi, UAE

6.7 Marketing Authorization Holder:

Neopharma, Abu Dhabi, UAE
Plot No. A1 89-95,
Industrial City of Abu Dhabi (ICAD),
Mussafah, Abu Dhabi, UAE