Levoflox 5mg/ml
Solution for I.V. Infusion

1. NAME OF THE MEDICINAL PRODUCT
Levoflox 5mg/ml Solution for I.V. Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
500 mg of levofloxacin (as hemihydrate) in a 100 ml glass bottle.
One ml of solution for infusion contains 5 mg of levofloxacin (as hemihydrate).
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
Solution for infusion.
Clear greenish-yellow solution.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
In adults for whom intravenous therapy is considered to be appropriate, Levoflox 5mg/ml is indicated for the treatment of the following infections when due to levofloxacin susceptible microorganisms:

- Community-acquired pneumonia.
- Complicated urinary tract infections including pyelonephritis.
- Skin and soft tissue infections.

Before prescribing Levoflox 5mg/ml, consideration should be given to national and/or local guidance on the appropriate use of fluoroquinolones.

4.2 Posology and method of administration
Levoflox 5mg/ml is administered by slow intravenous infusion once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. After initial use of the intravenous preparation the treatment may be completed with an oral presentation of levofloxacin and as considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology
The following dose recommendations can be given for Levoflox 5mg/ml:
Dosage in patients with normal renal function (creatinine clearance >50 ml/min)

Indication	**Daily dose regimen** *(according to severity)*	**Total duration of treatment**[1] *(according to severity)*
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
Skin and soft tissue infections	500 mg once or twice daily	7-14 days

[1] Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous to oral treatment depends on the clinical situation but is normally 2 to 4 days.

Special populations
Impaired renal function (creatinine clearance ≤50 ml/min)

	Dose regimen		
Creatinine clearance	**250 mg/24 h**	**500 mg/24 h**	**500 mg/12 h**

	first dose: 250 mg	*first dose:* 500 mg	*first dose:* 500 mg
50-20 ml/min	*then:* 125 mg/24 h	*then:* 250 mg/24 h	*then:* 250 mg/12 h
19-10 ml/min	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/12 h
<10 ml/min (including haemodialysis and CAPD)[1]	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/24 h

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

Impaired liver function
No adjustment of dosage is required since levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.

Elderly population
No adjustment of dosage 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
Levoflox 5mg/ml is contraindicated in children and growing adolescents (see section 4.3).

Method of administration
Levoflox 5mg/ml is only intended for slow intravenous infusion; it is administered once or twice daily. The infusion time must be at least 30 minutes for 250 mg or 60 minutes for 500 mg Levoflox 5mg/ml (see section 4.4).
For incompatibilities see section 6.2.

4.3 Contraindications

Levoflox 5mg/ml must not be used:

- in patients hypersensitive to levofloxacin or any other quinolone and 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

Risks of resistance
Methicillin-resistant *S. aureus* is 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).
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.

Infusion time
The recommended infusion time of at least 60 minutes for 500 mg Levoflox 5mg/ml should be observed. It is known for ofloxacin that during infusion tachycardia and a temporary decrease in blood pressure may develop. In rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin (*l*-isomer of ofloxacin), the infusion must be halted immediately.

Sodium content
This medicinal product contains 15.4 mmol sodium (354.20 mg) per 100 ml dose. To be taken into consideration by patients on a controlled-sodium diet.

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 of 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 pseudo-membranous 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 receiving 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 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 Levoflox 5 mg/ml 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.

Disglycaemia
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
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, 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 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 (see sections 4.2 Elderly population, 4.5, 4.8 and 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. Post-marketing 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 a more specific method. Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Aortic Aneurysm and Dissection
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in

patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department
The use of Levoflox 5 mg/ml should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with [INN] should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

4.5 Interactions with other medicinal products and other forms of interaction

Effect of other medicinal products on Levoflox 5mg/ml

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 was not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of Levoflox 5mg/ml 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on 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

Levoflox 5mg/ml 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 in this table are defined using the following convention: very common (1/10), common (1/100, <1/10), uncommon (1/1000, <1/100), rare (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.

System organ class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to <1/100)**	**Rare (≥1/10000 to <1/1000)**	**Very rare (<1/10000)**	**Not known (cannot be estimated from the available data)**
Infections and infestations		Fungal infection including Candida infection Pathogen resistance			
Blood and the 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 disorders		Anorexia	Hypoglycaemia particularly in diabetic patients (see section 4.4)		Hyperglycaemia Hypoglycaemic 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)

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)	Very rare (<1/10000)	Not known (cannot be estimated from the available data)
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) Uveitis
Ear and labyrinth disorders		Vertigo	Tinnitus		Hearing loss Hearing impaired
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	Phlebitis		Hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea			Bronchospasm Pneumonitis allergic
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation			Diarrhoea-haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudo-membranous colitis (see section 4.4) Pancreatitis

System organ class	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10000 to <1/1000)	Very rare (<1/10000)	Not known (cannot be estimated from the available data)
Hepatobiliary disorders	Hepatic enzyme increased (ALT/AST, alkaline phosphatase ,GGT)	Blood bilirubin increased			Jaundice and severe liver injury, including fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4) Hepatitis
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., Achilles tendon) Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)		Rhabdomyolysis Tendon rupture (e.g., Achilles tendon) (see 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	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.
Another undesirable effect which has been associated with fluoroquinolone administration includes: 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdosage of Levoflox 5mg/ml are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures, increases in QT interval.
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. 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 drug 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.

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
Pseudomonas spp.	≤1 mg/l	>2 mg/l
Acinetobacter spp.	≤1 mg/l	>2 mg/l
Staphylococcus spp.	≤1 mg/l	>2 mg/l
S. pneumoniae[1]	≤2 mg/l	>2 mg/l
Streptococcus A, B, C, G	≤1 mg/l	>2 mg/l
H. influenzae[2, 3]	≤1 mg/l	>1 mg/l
M. catarrhalis[3]	≤1 mg/l	>1 mg/l
Non-species related breakpoints[4]	≤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* is 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 desmethyllevofloxacin 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 is 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	20-49	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 photocarcinogenity study.
In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6 PHARMACEUTICAL PARTIC ULARS

6.1 List of excipients

Sodium chloride
Hydrochloride acid 37%
Water for injection.

6.2 Incompatibilities

In the absence of compatibility studies, Levoflox 5mg/ml solution for infusion must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.
Shelf life after removal of the outer packaging: 3 days (under indoor light conditions)
For the possibility of microbial contamination, the product should be used immediately. If the medication is not used immediately, the time and storage conditions during use of the product are the responsibility of the user.

6.4 Special precautions for storage

Keep the vial in the original packaging in order to protect from light (see section 6.3 "Shelf life"). Inspect visually prior to use. Only clear solutions without particles should be used.

Store below 25 ºC.

6.5 Nature and contents of container

100 ml, type II glass vial with chlorobutyl rubber stopper and tear-off alluminium lid. Each vial contains 100 ml solution for infusion.
Packs of 1, 5 and 25 vials.
Not all packs sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levoflox 5mg/ml solution for infusion should be used immediately after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during infusion.

This medicinal product is for single use only.

As for all medicines, any unused medicinal product should be disposed of accordingly and in compliance with local environmental regulations.

7 MARKETING AUTHORISATION HOLDER

Tec-O-Pharm-Libra LTD POB 45054, Jerusalem 91450

8 MANUFACTURER

Bioindustria Laboratorio Italiano Medicinali (signed Bioindustria L.I.M.) Via De Ambrosiis, 2 Novi Ligure (AL) – Italy.

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