SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Evoxil 5 mg/mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 5 mg of levofloxacin (as hemihydrate).

Each 50 mL vial of solution for infusion contains 250 mg of levofloxacin (as hemihydrate).

Each 100 mL vial of solution for infusion contains 500 mg of levofloxacin (as hemihydrate).

Excipients with known effect:
Each ml of solution for infusion contains 0.15 mmol (3.54 mg) sodium (as chloride)
50 mL of solution for infusion contains 7.70 mmol (177.10 mg) sodium (as chloride)
100 mL of solution for infusion contains 15.40 mmol (354.20 mg) sodium (as chloride)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

A clear greenish-yellow solution, free from foreign particles.

pH: 4.5 – 5.1

Osmolality: 290 mOsmol/Kg ± 5%

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be

prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection;
- other first-line antibiotics are contraindicated in an individual patient;
- other first-line antibiotics have caused side effects requiring treatment to be stopped;
- treatment with other first-line antibiotics has failed.

Evoxil solution for infusion is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

• Community-acquired pneumonia
• Complicated skin and soft tissue infections

For the above-mentioned infections Evoxil should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of these infections.

• Acute pyelonephritis and complicated urinary tract infections (see section 4.4)
• Chronic bacterial prostatitis
• Inhalation Anthrax: post-exposure prophylaxis and curative treatment (see

section 4.4) Consideration should be given to official guidance on the

appropriate use of antibacterial agents.

4.2 Posology and method of administration

Evoxil solution for infusion is administered by slow intravenous infusion once or twice daily. The dose depends on the type and severity of the infection and the susceptibility of the presumed causative pathogen. Treatment with Evoxil after initial use of the intravenous preparation may be completed with an appropriate oral presentation according to the SPC for the film-coated tablets and as considered appropriate for the individual patient. Given the bioequivalence of the parenteral and oral forms, the same dose can be used.

Posology

The following dose recommendations can be given for Evoxil:

Dose 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
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

[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)

Creatinine clearance	**Dose regimen**		
	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 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

Evoxil solution for infusion 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 Evoxil solution for infusion (see section 4.4).

For incompatibilities, see section 6.2 and compatibility with other infusion solutions, see section 6.6.

4.3 Contraindications

Evoxil solution for infusion must not be used:
• in patients hypersensitive to the active substance, any other quinolones or to any of the excipients listed in section 6.1,
• in patients with epilepsy,
• in patients with history of tendon disorders related to fluoroquinolone administration,
• in children or growing adolescents (up to age of 18),
• during pregnancy,
• in breast-feeding women.

4.4 Special warnings and precautions for use

The use of Evoxil should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolones containing products (see section 4.8). Treatment of these patients with Evoxil should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3)

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).

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.

Infusion time
The recommended infusion time of at least 30 minutes for 250 mg or 60 minutes for 500 mg Evoxil solution for infusion 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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Evoxil should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon). sometimes bilateral, may occur within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, in patients receiving daily doses of 1,000 mg of levofloxacin and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. 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. At the first sign of tendinitis (e.g. painful swelling,

inflammation) the treatment with Evoxil should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Myoclonus

Cases of myoclonus have been reported in patients receiving levofloxacin (see section 4.8). The risk of myoclonus is increased in older patients, and in patients with renal impairment if the dose of levofloxacin is not adjusted as per the creatinine clearance. Levofloxacin should be discontinued immediately at the first occurrence of myoclonus and appropriate treatment should be initiated.

Blood disorders

Bone marrow failure including leukopenia, neutropenia, pancytopenia, haemolytic anaemia, thrombocytopenia, aplastic anaemia, or agranulocytosis may develop during treatment with levofloxacin (see section 4.8). If any of these blood disorders is suspected, blood counts should be monitored. In case of abnormal results, discontinuation of treatment with levofloxacin should be considered.

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 cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with levofloxacin (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions, and be closely monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of levofloxacin, treatment with levofloxacin must not be restarted in this patient at any time.

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Prevention of photosensitisation
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 medicinal products 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.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

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 medicinal products that are known to prolong the QT interval (e.g.

Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medicinal products. 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
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Evoxil should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition. (see section 4.8)

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 test
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.

Sodium content
This medicinal product contains 177.10 mg sodium per 250 mg dose and 354.20 mg sodium per 500 mg dose, equivalent to 8.85 % and 17.71 % of the WHO recommended maximum daily intake for sodium, respectively.
The maximum daily dose of this product is equivalent to 35.42% of the WHO recommended maximum daily intake for sodium.
Evoxil is considered high in sodium. This should be particularly taken into account for

those on a low salt diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on levofloxacin

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 medicinal products 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 medicinal products 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 medicinal products: 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).

Medicinal products known to prolong QT interval

Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving medicinal products 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 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 section 4.2 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 the experimental data suggests 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 8,300 patients and on extensive post-marketing experience.

Frequencies in this table are defined using the following convention:
Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <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	Bone marrow failure including aplastic anaemia, 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)
Endocrine disorders			Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)	
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) Mania

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)**
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 Myoclonus
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
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

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)**
Gastrointestinal disorders	Diarrhoea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranus colitis (see Section4.4) 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
Skin and subcutaneous tissue disorders [b]		Rash Pruritus Urticaria Hyperhidrosis	Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) (see section 4.4), Fixed drug eruption	Toxic epidermal necrolysis Stevens-Johnson syndrome Erythema multiforme Photosensitivity reaction (see section 4.4) Leukocytoclastic vasculitis Stomatits Skin hyperpig mentation
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendon disorders (see sections 4.3 and 4.4) including tendinitis (e.g. Achilles tendon) Tendon rupture (e.g. Achilles tendon) (see sections 4.3 and 4.4)’	Rhabdomyolysis Ligament rupture Muscle rupture Arthritis

			Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4)	
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.

*Cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, fatigue, psychiatric symptoms, memory impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category).
** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

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 via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. By reporting side effects you can help provide more information on the safety of this medicine.

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 Evoxil solution for infusion are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, convulsive seizures, increases in QT interval as well as gastro-intestinal reactions such as nausea and mucosal erosions.
CNS effects including confusional state, convulsion, myoclonus, 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:	Anti-infectives for systemic use – Antibacterials for systemic use – 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.

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* 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 dose regimen.

Distribution
Approximately 30 - 40 % of levofloxacin is bound to serum protein.
The mean volume of distribution of levofloxacin is approximately 100 L after single and repeated 500 mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids
Levofloxacin has been shown to penetrate into bronchial mucosa, epithelial lining fluid, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue and urine. However, levofloxacin has poor penetration intro cerebro-spinal fluid.

Biotransformation
Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose 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 ($t_{½}$: 6 - 8 h). Excretion is primarily by the renal route (> 85 % of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/- 29.2 mL/min.

There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity
Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1,000 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 - 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 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 foetuses 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 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

Sodium chloride

Hydrochloric acid 5N (for pH adjustment)

Water for injection

6.2 Incompatibilities

Evoxil solution for infusion must not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate).

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years
Shelf life after removal of the outer packaging: 3 days (under indoor light conditions)
Shelf life after perforation of the rubber stopper: immediate use (see section 6.6)

After first opening:
From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

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

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

50 mL, type I transparent glass vial sealed with bromobutyl rubber stopper and an aluminium cap. Each vial contains 50 mL solution. Packs of 1 and 5 and 20 vials are available.

100 mL, type I transparent glass vial sealed with bromobutyl rubber stopper and an aluminium cap. Each vial contains 100 mL solution. Packs of 1, 5 and 20 vials are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused solution.

The product should be inspected visually for particles and discoloration prior to administration. Only clear, greenish-yellow solution, free from particles must be used.

Evoxil solution for infusion should be used immediately (within 3 hours) after perforation of the rubber stopper in order to prevent any bacterial contamination. No protection from light is necessary during the infusion.

Mixture with other solutions for infusion
Evoxil solution for infusion is compatible with the following solutions for infusion:
0.9% sodium chloride solution
5% dextrose injection
2.5% dextrose in Ringer's solution
Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes)

Chemical and physical compatibility of Evoxil solution for infusion with the above solutions have been demonstrated for 4 hours at room conditions.

See section 6.2 for incompatibilities.

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

7 MARKETING AUTHORISATION HOLDER

Kent Pharma UK Limited, 2nd Floor, Connect 38, 1 Dover Place, Ashford, Kent,

England,TN23 1FB.

8 MARKETING AUTHORISATION NUMBER(S)

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