SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Levofloxacin 5 mg/mL Solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s) with known effect:
100 mL of solution for infusion contains 15.4 mmol (354.2 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear greenish-yellow solution.
The osmolality of the solution for infusion is approximately 300 mOsm/kg.
The pH of the solution for infusion is approximately 4.8.

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.

Levofloxacin 5 mg/mL Solution for infusion is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- 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).
- Community-acquired pneumonia
- Complicated skin and soft tissue infections

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Levofloxacin 5 mg/mL Solution for infusion 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. Treatment with Levofloxacin 5 mg/mL Solution for infusion 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 dosage can be used.

Posology

The following dose recommendations can be given for Levofloxacin 5 mg/mL Solution for infusion:

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
Acute 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)

	Dose regimen		
	250 mg/24 h	**500 mg/24 h**	**500 mg/12 h**
Creatinine clearance	*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 dosage is required in the elderly, other than that imposed by consideration of renal function (See section 4.4 “Tendonitis and tendon rupture” and “QT interval prolongation”).

Paediatric population
Levofloxacin 5 mg/mL Solution for infusion is contraindicated in children and growing adolescents (see section 4.3).

Method of administration
Levofloxacin 5 mg/mL 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 Levofloxacin 5 mg/mL 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

Levofloxacin 5 mg/mL Solution for infusion must not be used:

- in patients hypersensitive to levofloxacin or any other quinolone or any of the excipients listed in section 6.1,
- in patients with epilepsy,
- in patients with history of tendon disorders related to fluoroquinolone administration,
- in children or growing adolescents,
- during pregnancy,
- in breast-feeding women.

4.4 Special warnings and precautions for use

The use of levofloxacin 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 levofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

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. Levofloxacin 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.

Risks of resistance
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 Levofloxacin 5 mg/mL 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.

Tendonitis and tendon rupture
Tendonitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as 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 tendonitis and tendon rupture is increased in patients receiving daily doses of 1000 mg levofloxacin, in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendonitis (e.g. painful swelling, inflammation) the treatment with levofloxacin 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.

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 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 Levofloxacin 5 mg/mL Solution for infusion 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, occurring more frequently in the elderly, 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). Levofloxacin treatment should be stopped immediately if a patient reports blood glucose disturbance and alternative nonfluoroquinolone antibacterial therapy should be considered.

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 immediately at the first signs or symptoms of these reactions and patients should be advised to contact their prescriber for advice. Alternative non fluoroquinolone antibacterial therapy should be considered, 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., hypokalaemia, 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, 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 levofloxacin 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.

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 (see section 4.8).

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.

Acute pancreatitis
Acute pancreatitis may be observed in patients taking levofloxacin. Patients should be informed of the characteristic symptoms of acute pancreatitis. Patients experiencing nausea, malaise, abdominal discomfort, acute abdominal pain or vomiting should have a prompt medical evaluation. If acute pancreatitis is suspected, levofloxacin should be discontinued; if confirmed, levofloxacin should not be restarted. Caution should be exercised in patients with a history of pancreatitis (see section 4.8).

Sodium content
This medicinal product contains 7.7 mmol (177.1 mg) sodium per 50 mL dose and 15.4 mmol (354.2 mg) sodium per 100 mL dose, equivalent to 8.85 % and 17.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on Levofloxacin 5 mg/mL Solution for infusion

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 co-administered with drugs that affect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

Clinical pharmacology studies have shown that the pharmacokinetics of levofloxacin were not affected to any clinically relevant extent when levofloxacin was administered together with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine.

Effect of Levofloxacin 5 mg/mL Solution for infusion on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33% when co-administered 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 is limited amount of data from the use of levofloxacin in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). However in the absence of human data and due to that experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in pregnant women (see sections 4.3 and 5.3).

Breastfeeding
Levofloxacin 5 mg/mL Solution for infusion 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

Levofloxacin has minor or moderate influence on the 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 most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below.
The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**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	**Frequency not known** (cannot be estimated from the available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section 4.4)
Endocrine Disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Psychiatric Disorders*		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	
Nervous System Disorders*		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus see section 4.4) Vertigo	Migraine coordination Disturbance Gait disturbance Olfactory nerve disorders Intracranial Hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye Disorders*			Visual Disturbances (e.g. diplopia)	Visual colour distortions	
Ear and Labyrinth Disorders*			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders**			Tachycardia		Ventricular arrhythmia, torsades de pointes (reported predominantly in patients with risk

					factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9).
Vascular Disorders**			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders*		Musculoskeletal pain (e.g. extremity pain,	Myalgia Arthritis Increased muscle tone and	Muscular weakness Exacerbation of symptoms of	

		back pain, chest pain) Arthralgia	cramping Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4)	myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

*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).

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric population

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

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
Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

According to toxicity studies in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected following acute overdose of levofloxacin 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.

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for levofloxacin and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx"

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 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 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 – 8h). Excretion is primarily by the renal route (> 85 % of the administered dose).

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

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

Linearity

Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.

Special populations

Subjects with renal insufficiency

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function renal elimination and clearance are decreased, and elimination half-lives increased as shown in the table below:

Pharmacokinetics in renal insufficiency following single oral 500 mg dose:

Cl_{cr} [mL/min]	< 20	20 – 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 PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injection
(Na^+ concentration: 154 mmol / L).

6.2 Incompatibilities

This medicinal product 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 pouch or carton: To be used immediately after removing the bottles from the pouch or carton.

Dilution is not necessary prior to administration.
For the diluted product chemical and physical in use stability has been demonstrated for 2 hours at 25°C.

From a microbiological point of view, the solution for infusion should be used immediately once opened. If not used immediately, in-use storage times and conditions are the responsibility of the user, unless reconstitution/dilution has taken place in controlled and validated conditions.

6.4 Special precautions for storage

Overwrapped bottles: Keep the bottle in the outer pouch in order to protect from light. To be used immediately after removing from the pouch (see section 6.3).
Bottles without overwrapping should be kept in the carton in order to protect from light. To be used immediately after removing from the carton (see section 6.3).
No protection from light is required during the infusion.
Inspect visually prior to use. Only clear solutions without particles should be used.

6.5 Nature and contents of container

100 mL plastic bottles of polypropylene, with a molded plastic cap, a rubber (type II) gasket and a pull ring, or a twin port cap, which includes a rubber gasket (Type II) on the inside and two pull rings in the outside. Each bottle is placed in a metalized plastic pouch. Packs of 10 bottles are available.

Alternatively

100 mL plastic bottles of polypropylene, with a molded plastic cap, a rubber (type II) gasket and a pull ring, or a twin port cap, which includes a rubber gasket (Type II) on the inside and two pull rings in the outside. Bottles are placed in carton. Packs of 1 or 10 bottles are available.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Levofloxacin 5 mg/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.

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

For single use only.

Mixture with other solutions for infusion:
Levofloxacin 5 mg/mL Solution for infusion is compatible with the following solutions for infusion when diluted at a range of concentrations (0.5 – 4 mg/mL):

- 0.9 % (9 mg/mL) sodium chloride solution.

- 5% (50 mg/mL) dextrose injection.
- 2.5 % (25 mg/mL) dextrose in Ringer solution.

Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).
Levofloxacin 5 mg/mL Solution for infusion may be given alone or with one of the above mentioned infusions.
See section 6.2 for incompatibilities.

7. MARKETING AUTHORISATION HOLDER

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Evagorou & Makariou, Mitsi Building 3,
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Cyprus

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