Summary of Product Characteristic

Lequinox

1. Name of the Medicinal Product

Lequinox 5 mg/mL Solution for infusion

2. Quality and Quantitative Composition

Each mL contains Levofloxacin 5 mg

3. Pharmaceutical Form

Solution for infusion.

4. Clinical Particulars

4.1 Therapeutic indication

Levofloxacin is indicated for the treatment of adults (≥16 years of age) with mild, moderate and severe infection caused by susceptible strains of the designated microorganisms in the conditions listed below, when intravenous administration offers a route of administration advantageous to the patient (e.g., patient cannot tolerate an oral dosage form).

1. Community-acquired pneumonia due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila* or Mycoplasma pneumoniae.

2. Nosocomial pneumonia due to methicillin-susceptible *Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,* or *Streptococcus pneumoniae*. Adjunctive therapy should be used as clinically indicated. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

3. Uncomplicated skin and skin structure infections (mild to moderate) including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus* or *Streptococcus pyogenes*.

4. Complicated skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes* or *Proteus mirabilis*.

5. Urinary tract infections (mild to moderate) due to *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Pseudomonas aeruginosa* or *Staphylococcus saprophyticus*.

6. Pyelonephritis (mild to moderate) caused by *Escherichia coli*.

7. Acute bacterial sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis*.

8. Acute bacterial exacerbation of chronic bronchitis caused by methicillin-susceptible *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, or Moraxella catarrhalis.*

9. Chronic bacterial prostatitis caused by *Escherichia coli*, *Enterococcus faecalis,* or methicillin-susceptible *Staphylococcus epidermidis*.

10. Inhalational anthrax postexposure prophylaxis and curative treatment: 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.

Reference 1: Package insert, Cravit® i.v., Daiichi Sankyo (Thailand), Indications and usage
Reference 2: Prescribing information, Levaquin® , Indications and usage
Reference 3: Drug Facts & Comparison, 2017, P.3041, Levofloxacin - injection, Indication
Reference 4: SmPC, Levofloxacin 5 mg/ml Solution for Infusion, Therapeutic indications, Hospira UK Ltd

4.2 Posology and method of administration

Lequinox should only be administered by intravenous infusion. It is not for intramuscular, intrathecal, intraperitoneal, or subcutaneous administration. The dosage depends on the type and severity of the infection and the sensitivity of the presumed causative pathogen. The duration of therapy varies according to the course of the disease. As with antibiotic therapy in general, administration of Lequinox should be continued for a minimum of 48 to 72 hours after the patient has become afebrile of evidence of bacterial eradication has been obtained. It is usually possible to switch from initial intravenous treatment to the oral route after a few days.

Posology The following dose recommendations can be given for levofloxacin.

Patient with normal renal function (creatinine clearance > 80 mL/min)

Infection	Dosed every 24 hours (Dose per day)	Duration	Daily Dose
Community-acquired pneumonia	500 mg 750 mg	7-14 days 5 days	500 mg 750 mg
Nosocomial pneumonia	750 mg	7-14 days	750 mg
Uncomplicated skin and skin structure infections	500 mg	7-10 days	500 mg
Complicated skin and skin structure infections	750 mg	7-14 days	750 mg
Urinary tract infections	250 mg	10 days	250 mg
Urinary tract infections, complicated	750 mg	5 days	750 mg
Pyelonephritis	250 mg	10 days	250 mg
Acute pyelonephritis	750 mg	5 days	750 mg
Acute bacterial sinusitis	750 mg 500 mg	5 days 10-14 days	750 mg 500 mg
Acute bacterial exacerbation of chronic bronchitis	500 mg	7 days	500 mg
Chronic bacterial prostatitis	500 mg	28 days	500 mg
Inhalational Anthrax	500 mg	56 days	500 mg

Special population

Patient with impaired renal function

No adjustment is necessary for patients with a creatinine clearance ≥ 50 ml/min.

In patient with impaired renal function (creatinine clearance < 50 ml/min) adjustment of the dosage regimen is necessary to avoid the accumulation of levofloxacin due to decreased clearance.

Dosage adjustment in adult patients with renal impairment (creatinine clearance < 50 ml/min)

Dosage in normal Renal function every 24 hours	**Creatinine clearance 20-49 ml/min**	**Creatinine clearance 10-19 ml/min**	**Hemodialysis or chronic ambulatory peritoneal dialysis (CAPD)**
750 mg	750 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours	750 mg initial dose, then 500 mg every 48 hours
500 mg	500 mg initial dose, then 250 mg every 24 hours	500 mg initial dose, then 250 mg every 48 hours	500 mg initial dose, then 250 mg every 48 hours
250 mg	No dosage adjustment required	250 mg every 48 hours. If treating uncomplicated UTI, then no dosage adjustment is required	No information on dosing adjustment is available

Patients with hepatic impairment

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

Older people

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').

Pediatric population

Levofloxacin is contraindication in children and growing adolescents.

Method of administration

Lequinox injection should be slowly intravenous infusion; it is administered once or twice daily. The infusion time must be at least 60 minutes for 250 mg and 500 mg or 90 minutes for 750 mg levofloxacin. For incompatibilities see 6.2 and compatibility with other infusion see 6.6.

Reference 1: Package insert, Cravit® i.v., Daiichi Sankyo (Thailand), Dosage and administration
Reference 2: Prescribing information, Levaquin® , Dosage and administration
Reference 3: Drug Facts & Comparison, 2017, P.3042-3043, Levofloxacin - injection, Administration and dosage
Reference 4: SmPC, Levofloxacin 5 mg/ml Solution for Infusion, Posology and method of administration, Hospira UK Ltd

4.3 Contraindications

Lequinox must not be used:

- in patients hypersensitive to levofloxacin, to 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
- during pregnancy
- in breast-feeding women

Reference 4: SmPC, Levofloxacin 5 mg/ml Solution for Infusion, Contraindication, Hospira UK Ltd

4.4 Special warning 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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. 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.

Methicillin-resistant *Staphylococcus aureus* (MRSA) 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.

Infusion time

The recommended infusion time of at least 60 minutes for 250 mg and 500 mg or 90 minutes for 750 mg levofloxacin 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 23.4 mmol (531 mg) sodium per 150 mL dose, 15.4 mmol (354 mg) sodium per 100 mL dose and 7.7 mmol (177 mg) sodium per 50 mL dose. To be taken into consideration by patients on a controlled sodium diet.

Tendinitis and tendon rupture

Tendinitis 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 tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, in patients receiving daily doses of 1000 mg levofloxacin and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (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., immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

***Clostridium difficile*-associated disease**

Diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with levofloxacin, (including several weeks after treatment) may be symptomatic of *Clostridium difficile*-associated disease (CDAD). CDAD may range in severity from mild to life threatening, the most severe form of which is pseudomembranous colitis. It is therefore important to consider this diagnosis in patients who develop serious diarrhea during or after treatment with levofloxacin. If CDAD is suspected or confirmed, levofloxacin should be stopped immediately and appropriate treatment initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Patients predisposed to seizures

Quinolones may lower the seizure threshold and may trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy and, as with other quinolones, should be used with extreme caution in patients predisposed to seizures, or concomitant treatment with active substances which lower the cerebral

seizure threshold, such as theophylline. In case of convulsive seizures, treatment with levofloxacin should be discontinued.

Patients with G-6- phosphate dehydrogenase deficiency

Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents. Therefore, if levofloxacin has to be used in these patients, potential occurrence of hemolysis should be monitored.

Patients with renal impairment

Since levofloxacin is excreted mainly by the kidneys, the dose medicinal product should be adjusted in patients with renal impairment.

Hypersensitivity reactions

Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g., angioedema up to anaphylactic shock), occasionally following the initial dose. Patients should discontinue treatment immediately and contact their physician or an emergency physician, who will initiate appropriate emergency measures.

Severe bullous reactions

Cases of severe bullous skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Levofloxacin. Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Dysglycaemia

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

Prevention of photosensitization

Photosensitization has been reported with levofloxacin. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial ultraviolet (UV) rays (e.g. sunray lamp, solarium), during treatment and for 48 hours following treatment discontinuation, in order to prevent photosensitization.

Patients treated with Vitamin K antagonists

Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g., warfarin), coagulation tests should be monitored when these drugs are given concomitantly.

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behavior - sometimes after only a single dose of levofloxacin. In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. 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, hypomagnesaemia)
- cardiac disease (e.g., heart failure, myocardial infarction, bradycardia)
- elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations.

Peripheral neuropathy

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.

Hepatobiliary disorders

Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, primarily in patients with severe underlying diseases, e.g., sepsis. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Exacerbation of myasthenia gravis

Fluoroquinolones, including levofloxacin, have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. 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.

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.

Vascular disorders

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.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method. Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Special warnings and precautions for use, Hospira UK Limited

Warning (based on Notification of the Ministry of Public Health)

1. Do not use the drug in patients with a history of hypersensitivity to the drug or any other quinolones.
2. Pregnant women and breastfeeding women should avoid the use of this drug.
3. If the symptoms of rash, malaises, myalgia, arthralgia and tendonitis had occurred after the administration of the drug, the patient should discontinue this drug and consult the physician immediately.
4. The drug may cause hepatic and renal toxicities.
5. Do not use this drug or used with caution patients with central nervous system (CNS) disorder that may predispose to seizure dosing dependent.

6. This drug may cause prolongation of QT interval, so this drug should be used with caution in patient who has risks of prolongation of QT interval including geriatric, cardiac disease especially arrhythmia, hypertension, and hypokalemia.
7. Avoided using this drug with other drugs that cause prolongation of QT interval including antiarrhythmic, class IA (quinidine, procainamide). Class III (amiodarone), cisapride, erythromycin, antipsychotics, and tricyclic antidepressants
8. This drug may cause phototoxicity reaction including Toxic Epidermal Necrolysis, Stevens-Johnson syndrome, and Erythema Multiforme.
9. This drug should be used with caution in diabetic patient because this drug may cause dysglycemia.
10. Concomitant used of this drug and warfarin may increase the activities of warfarin.

Reference 5: Notification of the Ministry of Public Health

4.5 Interaction with other medicinal products and other forms of interactions

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, nonsteroidal 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 effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Other relevant information

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

Effect of Levofloxacin on other medicinal products

Ciclosporin

The half-life of ciclosporin was increased by 33% when 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.

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, and antipsychotics).

Other relevant information

In a pharmacokinetic interaction study, levofloxacin did not affect the pharmacokinetics of theophylline (which is a probe substrate for CYP1A2), indicating that levofloxacin is not a CYP1A2 inhibitor.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Interaction with other medicinal products and other forms of interaction, Hospira UK Limited

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast Feeding

Levofloxacin is contraindicated in breast-feeding women. There is insufficient evidence on the excretion of Levofloxacin in human milk, however other fluoroquinolones are excreted in human breast milk. In the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, levofloxacin must not be used in breast-feeding women.

Fertility

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

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Fertility, pregnancy and lactation, Hospira UK Limited

4.7 Effects on ability to drive and use machine

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).

Reference 1: SmPC, Levofloxacin 5 mg/ml solution for infusion, Effects on ability to drive and use machines, Hospira UK Limited

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 the lymphatic system disorders		Leukopenia Eosinophilia	Thrombocytopenia Neutropenia	Pancytopenia Agranulocytosis Hemolytic anemia
Immune system disorders			Angiodema Hypersensitivity	Anaphylactic[a] shock and Anaphylactoid[a] shock
Metabolism and nutrition disorders		Anorexia	Hypoglycemia particularly in diabetic patients	Hyperglycemia Hypoglycemic coma
Psychiatric disorders*	Insomnia	Anxiety Confusional state Nervousness	Psychotic reactions (with hallucination, paranoia) Depression Agitation Abnormal dreams Nightmares	Psychotic with self-endangering behavior including suicidal ideation or suicide attempt
Nervous system disorders*	Headache Dizziness	Somnolence Tremor Dysgeusia	Convulsion Paresthesia	Peripheral sensory neuropathy Peripheral sensory

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)
				motor neuropathy Parosmia including anosmia Dyskinesia Extrapyramidal disorder Ageusia Syncope Benign intracranial Hypertension
Eye disorders*			Visual disturbances such as blurred vision	Transient vision loss
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
Vascular disorders	Phlebitis		Hypotension	
Respiratory, thoracic and mediastinal disorders		Dyspnea		Bronchospasm Pneumonitis allergic
Gastro-intestinal disorders	Diarrhea Vomiting Nausea	Abdominal pain Dyspepsia Flatulence Constipation		Diarrhea – hemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis Pancreatitis
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 Hepatitis
Skin and subcutaneous tissue disorders[b]		Rash Pruritus Urticaria Hyperhidrosis		Toxic epidermal necrolysis Stevens-Johnson syndrome

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)
				Erythema multiforme Photosensitivity Reaction Leukocytoclastic vasculitis Stomatitis
Musculoskeletal and connective tissue disorders*		Arthralgia Myalgia	Tendon disorders including tendinitis (e.g., Achilles tendon, Muscular weakness which may be of special importance in patients with myasthenia gravis	Rhabdomyolysis Tendon rupture (e.g. Achilles tendon) 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)

* Very rare 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 paresthesia, depression, fatigue, memory impairment, sleep disorders, 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

[a] Anaphylactic and anaphylactoid reactions may sometimes occur, even after the first dose.

[b] Mucocutaneous reactions may sometimes occur even after the first dose.

Other undesirable effects which have been associated with fluoroquinolone administration include:

• attacks of porphyria in patients with porphyria.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Undesirable effects, Hospira UK Limited

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. Hemodialysis, including peritoneal dialysis and CAPD, are not effective in removing levofloxacin from the body. No specific antidote exists.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Overdose, Hospira UK Limited

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 (Cmax) 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 topisomerase 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 MIC's of 0.12-0.5 mg/L) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with *H. influenzae*.

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

[4] Breakpoints apply to an oral dose of 500 mg x1 to 500 mg x2 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.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Pharmacodynamic properties, Hospira UK Limited

5.2 Pharmacokinetics 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 to 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 cerebrospinal 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 (t½: 6 – 8 h). Excretion is primarily by the renal route (> 85 % of the administered dose). The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175+/- 29.2 ml/min. There are no major differences in the pharmacokinetics of levofloxacin following intravenous and oral administration, suggesting that the oral and intravenous routes are interchangeable.

Linearity

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

Special Populations

Subjects with renal insufficiency

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

Pharmacokinetics in renal insufficiency following single oral 500 mg dose

Cl_{cr} [ml/min]	< 20	20 - 40	50 - 80
Cl_R [ml/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

Elderly subjects

There are no significant differences in levofloxacin kinetics 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.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Pharmacokinetic properties, Hospira UK Limited

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 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 lung (CHL) 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 tumor development in a photocarcinogenicity assay. 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.

Reference 4: SmPC, Levofloxacin 5 mg/ml solution for infusion, Preclinical safety data, Hospira UK Limited

6. Pharmaceutical Particulars

6.1 List of excipients

Sodium chloride

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with heparin or alkaline solutions (e.g., sodium hydrogen carbonate). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years

Chemical and physical in use stability has been demonstrated for 3 days at store below 30^{o}C, if the drug removal of the outer packaging and exposed to light.

Chemical and physical in use stability has been demonstrated for 3 hours at store below 30^{o}C, after perforation of the rubber stopper.

6.4 Special precautions for storage

Store below 30 ºC. Keep the bag in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Plastic bottle (Polypropylene) size 50, 100 and 150 ml with or without paper box of 1, 5, 10, 12, 20, 24 and 50 bottles.

Plastic bag (Polypropylene) size 50, 100 and 150 ml are packed or unpacked in sachet of 1 bag and with or without paper box of 1, 5, 10, 12, 20, 24 and 50 bags.

6.6 Special precautions for disposal and other handling

This product is for single use only.

No protection from light is necessary during infusion.

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

Mixture with other solutions for infusion:

Levofloxacin 5mg/ml Solution for Infusion is compatible with the following solutions for infusion:

• Sodium chloride 9 mg/ml (0.9%) solution

• Dextrose 50 mg/ml (5%) injection

• Dextrose 50 mg/ml (5%) in lactated Ringer's solution

• Dextrose 25 mg/ml (2.5%) in Ringer's solution

• Combination solutions for parenteral nutrition (amino acids, carbohydrates, electrolytes).

The solution should be visually inspected prior to use. It must only be used if the solution is clear, practically free from particles.

7. Marketing Authorization Holder

ABLE MEDICAL COMPANY LIMITED

111 Moo. 9 Nong Son, Chiang Yuen,

Mahasarakham 44160, Thailand

8. Marketing Authorization Numbers

xx xxx/xx

9. Date of authorization

DD/MM/YYYY

10. Date of revision of the text

24 May, 2021