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

Indication	**Daily dose regimen** *(according to severity)*	**Total duration of treatment[1](according to severity)**
Community-acquired pneumonia	500 mg once or twice daily	7-14 days
Pyelonephritis	500mg once daily	7-10 days
Complicated urinary tract infections	500mg once daily	7-14 days
Chronic bacterial prostatitis	500mg once daily	28 days
Complicated skin and soft tissue infections	500 mg once or twice daily	7-14 days
Inhalation anthrax	500mg once daily	8weeks

[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		
	50 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)	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/24 h

Impaired liver function

No adjustment of dose is required since levofloxacin is not metabolised to any relevant extent by the liver and is mainly excreted by the kidneys.

Elderly population

No adjustment of dose is required in the elderly, other than that imposed by consideration of renal function.

Paediatric population

Levofloxacin is contraindicated in children and growing adolescents

Method of administration

Levofloxacin solution for infusion is only intended for slow intravenous infusion; it is

• In breast-feeding women

4.4 Special warnings and precautions for use

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. 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 30 minutes for 250 mg or 60 minutes for 500 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.

Tendinitis and tendon rupture

Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendinitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin and have been reported up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in patients aged over 60 years, in patients receiving daily doses of 1000mg and in patients using corticosteroids. The daily dose should be adjusted in elderly patients based on creatinine clearance.Close monitoring of these patients is therefore necessary if they are prescribed

levofloxacin. All patients should consult their physician if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon

Clostridium difficile-associated disease

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

Patients predisposed to seizures

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

Dysglycaemia

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

Prevention of photosensitisation

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

Patients treated with Vitamin K antagonists

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

Psychotic reactions

Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour - sometimes after only a single dose of levofloxacin . In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. 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, 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 fluoroquiolones, including levofloxacin, in these populations.

Peripheral neuropathy

Peripheral sensory neuropathy and peripheral motor sensory neuropathy have been reported in patients receiving fluoroquinolones, including levofloxacin, which can be rapid in its onset. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy in order to prevent the development of an irreversible condition.

Hepatobiliary disorders

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

Exacerbation of myasthenia gravis

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

reactions, including deaths and the requirement for respiratory support, have been associated with fluoroquinolone use in patients with myasthenia gravis. Levofloxacin is not recommended in patients with a known history of myasthenia gravis.

Vision disorders

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

Superinfection

The use of levofloxacin, especially if prolonged, may result in overgrowth of non-susceptible organisms. If superinfection occurs during therapy, appropriate measures should be taken.

Interference with laboratory tests

In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

Levofloxacin may inhibit the growth of *Mycobacterium tuberculosis* and, therefore, may give false-negative results in the bacteriological diagnosis of tuberculosis.

4.5 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 . 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.

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 Side effects

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience.

Frequencies in this table are defined using the following convention:	
Very common	(≥1/10),
Common	(≥1/100 to <1/10),
Uncommon	(≥1/1000 to <1/100),
Rare	(≥1/10000 to <1/1000),
Very rare:	(< 1/10000) ,
Not known	(Cannot be estimated from the available data).

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

Infections and infestations:

Uncommon: Fungal infection including Candida infection

Blood and the lymphatic system disorders

Uncommon: Leukopenia, Eosinophilia

Rare: Thrombocytopenia, Neutropenia

Not known: Pancytopenia, Agranulocytosis, Haemolytic anaemia

Immune system disorders

Rare: Angiodema, Hypersensitivity

Not known : Anaphylactic shock and Anaphylactoid shock

Metabolism and nutrition disorders

Uncommon: Anorexia

Rare: Hypoglycaemia particularly in diabetic patients

Not known: Hyperglycaemia, Hypoglycaemic coma

Psychiatric disorders

Common: Insomnia

Uncommon: Anxiety, Confusional state, Nervousness

Rare: Psychotic reactions (with eg hallucination, paranoia), Depression, Agitation, Abnormal dreams, Nightmares

Not known: Psychotic with self-endangering behaviour including suicidal ideation or suicide, attempt.

Nervous system disorders

Common: Headache, Dizziness

Uncommon: Somnolence, Tremor, Dysgeusia

Rare: Convulsion , Paraesthesia

Not known: Peripheral sensory neuropathy , Peripheral sensory motor neuropathy , Parosmia including anosmia, Dyskinesia, Extrapyramidal disorder, Ageusia, Syncope, Benign intracranial hypertension.

Eye disorders

Rare: Visual disturbances such as blurred vision

Not known: Transient vision loss

Ear and Labyrinth disorders

Uncommon: Vertigo

Rare: Tinnitus

Not known: Hearing loss, Hearing impaired

Cardiac disorders

Rare: Tachycardia, Palpitation

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

Vascular disorders

Common: Phlebitis

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Not known: Bronchospasm, Pneumonitis allergic

Gastro-intestinal disorders

Common: Diarrhoea, Vomiting, Nausea

Uncommon: Abdominal pain, Dyspepsia, Flatulence, Constipation

Not known: Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, Pancreatitis

Hepatobiliary disorders

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

Uncommon: Blood bilirubin increased

Not known: Jaundice and severe liver injury, including fatal cases with acute liver failure , primarily in patients with severe underlying diseases, Hepatitis.

Skin and subcutaneous tissue disorders

Uncommon: Rash, Pruritus, Urticaria, Hyperhidrosis

Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction , Leukocytoclastic vasculitis, Stomatitis

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia, Myalgia

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

Not known: Rhabdomyolysis, Tendon rupture (e.g. Achilles tendon) Ligament rupture, Muscle rupture, Arthritis.

Renal and Urinary disorders

Uncommon: Blood creatinine increased

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

General disorders and administration site conditions

Common: Infusion site reaction (pain, reddening)

Uncommon: Asthenia

Rare: Pyrexia

Not known: Pain (including pain in back, chest, and extremities)

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 over dosage 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 topisomeras 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 500mg x1 to 500mg x2 and an intravenous dose of 500mg x 1 to 500mg 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, groups 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 Staphylococcusspp

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

Methicilin-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 to 100 %.

Food has little effect on the absorption of levofloxacin.

Steady state conditions are reached within 48 hours following a 500mg 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 100l after single and repeated 500mg doses, indicating widespread distribution into body tissues.

Penetration into tissues and body fluids:

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

Biotransformation

Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites account for < 5 % of the dose 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 500mg 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 500mg 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.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium chloride

DiSodium Edetate

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

24 months

6.4 Special precautions for storage

Do not store above 30°C and do not freeze.

6.5 Nature and contents of container

Pack sizes: 100 mL

The bottles Low Density Polyethylene plastic are overwrapped with a protective plastic pouch then packed in baby cartons

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).

See 6.2 for incompatibilities.

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

7. Marketing authorisation holder

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8. Marketing authorisation number

119/ID/NDA/03/13

9. Date of first authorisation/renewal of the authorisation

15th May 2014

10. Date of revision of the text

15/08/2016

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