

**PACKAGE LEAFLET**  
**for medical use of a medicinal product**

**LEFLOCK**

***Qualitative and quantitative composition: :***

*active substance:* levofloxacin;

1 tablet contains levofloxacin hemihydrate 250 mg or 500 mg related to levofloxacin;

*excipients:* cellulose microcrystalline, crospovidone, povidone, talc, magnesium stearate, hypromellose, titanium dioxide (E 171), macrogol 4000, sunset yellow FCF (E 110).

**Pharmaceutical form.** Film-coated tablets.

*Basic physical and chemical properties:*

250 mg tablets: pinkish, biconvex, film-coated tablets with a break line;

500 mg tablets: pinkish, oblong, biconvex, film-coated tablets with a break line.

**Pharmacotherapeutic group.**

Antibacterial agents for systemic use. Quinolone antibacterials. Fluoroquinolones. Levofloxacin. ATC Code J01M A12.

***Pharmacological properties.***

*Pharmacodynamic properties.*

Levofloxacin is a synthetic antibacterial agent from the group of fluoroquinolones, the S-enantiomer of a racemic mixture of ofloxacin. As a fluoroquinolone antibacterial agent, levofloxacin acts on the DNA-/DNA-gyrase complex and topoisomerase IV.

Resistance.

The main mechanism of resistance is caused by mutations in gyr-A genes. *In vitro*, there is cross-resistance between levofloxacin and other fluoroquinolones. Due to the mechanism of action, there is usually no cross-resistance between levofloxacin and other classes of antibacterial agents.

The prevalence of resistance may vary geographically and over time for individual species, therefore local information about resistance is important, especially in the treatment of severe infections. If necessary, expert advice should be sought when the local prevalence of resistance is such that the feasibility of using the drug, at least for some types of infections, is questionable.

Breakpoints.

The clinically defined minimum inhibitory concentration (MIC) limits recommended by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for determining the sensitivity of intermediately susceptible organisms and intermediately resistant microorganisms are shown in Table 1.

Table 1

EUCAST clinical MIC breakpoints for levofloxacin:

Pathogen	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤ 1 mg/L	> 2 mg/L

<i>Pseudomonas spp.</i>	≤ 1 mg/L	> 2 mg/L
<i>Acinetobacter spp.</i>	≤ 1 mg/L	> 2 mg/L
<i>Staphylococcus spp.</i>	≤ 1 mg/L	> 2 mg/L
<i>S. pneumoniae</i> <sup>1</sup>	≤ 2 mg/L	> 2 mg/L
<i>Streptococcus A, B, C, G</i>	≤ 1 mg/L	> 2 mg/L
<i>Haemophilus influenzae</i> <sup>2,3</sup>	≤ 1 mg/L	> 1 mg/L
<i>Moraxella catarrhalis</i> <sup>3</sup>	≤ 1 mg/L	> 1 mg/L
<i>Non-species related breakpoints</i> <sup>4</sup>	≤ 1 mg/L	> 2 mg/L

<sup>1</sup> The breakpoints for levofloxacin related to high dose therapy.

<sup>2</sup> Low-level resistance to fluoroquinolone (ciprofloxacin MICs of 0.12-0.5 mg/L) may occur, but there is no evidence that this resistance is of clinical importance in respiratory tract infections caused by *Haemophilus influenzae*.

<sup>3</sup> Strains with MIC values above the breakpoint between susceptible and intermediately susceptible (moderately resistant) strains are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any of those isolates should be repeated and if the result is confirmed, the isolate should 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 as resistant.

<sup>4</sup> Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.

### Antibacterial range.

The prevalence of resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections.

### 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: *Burkholderia cepacia*, *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*, *Chlamidia trachomatis*, *Legionella pneumophila*, *Mycoplasma pneumoniae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*.

### Species for which acquired (secondary) resistance may be a problem.

Aerobic gram-positive bacteria: *Enterococcus faecalis*, *Staphylococcus aureus* methicillin-resistant\*, *Staphylococcus coagulase 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* may be resistant to fluoroquinolones, in particular to levofloxacin.

### Pharmacokinetic properties.

#### Absorption.

There is no significant difference in the pharmacokinetics of levofloxacin after intravenous and oral administration.

Taken orally, levofloxacin is rapidly and almost completely absorbed, the maximum plasma concentration is reached 1-2 hours after administration. The absolute bioavailability is 99-100 %. Food has almost no effect on levofloxacin absorption. Steady-state conditions are reached within 48 hours with a dosage regimen of 500 mg 1 or 2 times a day.

#### Distribution.

Approximately 30–40 % of levofloxacin is bound to serum protein. The average volume of distribution of levofloxacin is approximately 100 l after a single and repeated dose of 500 mg, indicating wide distribution into body tissues.

There is almost no cumulative effect of repeated dosing of levofloxacin 500 mg once daily. Following dosing 500 mg twice daily, a minor but predictable cumulative effect is observed.

### Penetration into tissues and body fluids.

Levofloxacin has been shown to penetrate into bronchial mucosa, bronchial secretions of lung tissues, alveolar macrophages, lung tissue, skin (blister fluid), prostatic tissue, and urine. However, levofloxacin penetrates poorly into the cerebrospinal fluid.

### Biotransformation.

Levofloxacin is metabolized 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 administration levofloxacin is eliminated relatively slowly from the plasma (with a half-life of 6 to 8 h). The drug is excreted primarily by kidneys (>85 % of the dose administered). The total levofloxacin clearance after a single dose of 500 mg was  $175 \pm 29.2$  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 demonstrates linear pharmacokinetics in the dose range from 50 to 1000 mg.

### Patients with renal impairment.

The pharmacokinetics of levofloxacin are affected by renal impairment. With decreasing renal function, renal elimination and clearance are decreased, and elimination half-life increases as shown in Table 2.

Table 2

Creatinine clearance	< 20	20–49	50–80
Renal clearance (mL/min)	13	26	57
Elimination half-life (hours)	35	27	9

### Elderly.

There are no major 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 minor gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

## **Clinical particulars.**

### ***Therapeutic indications.***

Leflock tablets indicated for adults for the treatment of infectious and inflammatory diseases of mild to moderate severity caused by microorganisms susceptible to levofloxacin:

- acute bacterial sinusitis\*;
- exacerbation of chronic obstructive pulmonary disease, including bronchitis\*;
- community-acquired pneumonia\*;
- complicated urinary tract infections (including acute pyelonephritis);
- uncomplicated cystitis\*;
- chronic bacterial prostatitis;
- complicated skin and soft tissue infections\*;
- inhalation anthrax: post-exposure prophylaxis and curative treatment.

\*For the above-mentioned infectious diseases, levofloxacin should be administered only in cases of insufficient efficacy of other antibacterials, which are mainly used for the initial treatment of these infections.

This dosage form of levofloxacin can be used to complete the course of therapy in patients who have shown improvement in the course of primary treatment with levofloxacin in the form of an infusion solution.

Formal recommendations on the appropriate use of antibacterial agents should be considered.

### ***Contraindications.***

- Hypersensitivity to levofloxacin, other quinolones or to any of the excipients of the drug.
- Epilepsy.
- History of tendon disorders related to quinolone administration.

- Children (aged below 18 years).
- Pregnancy or breast-feeding.

### ***Interaction with other medicinal products and other forms of interaction.***

#### **Effect of other medicinal products on levofloxacin.**

*Iron salts, antacids containing magnesium and aluminum, didanosine.* Absorption of levofloxacin is significantly reduced when taken concomitantly with antacids containing magnesium and aluminum, as well as with drugs containing iron salts, or with didanosine (didanosine in a buffered tablet with aluminum or magnesium). Concomitant use of fluoroquinolones with multivitamins containing zinc leads to decreasing in their absorption. The recommended time interval between administration of levofloxacin and these medications should be at least 2 hours.

*Calcium salts.* Have a minimal effect on the levofloxacin absorption.

*Sucralfate.* Levofloxacin bioavailability is significantly reduced when used concomitantly with sucralfate. If the patient needs to receive both sucralfate and levofloxacin, sucralfate should be taken 2 hours after taking levofloxacin.

*Theophylline, fenbufen, or similar non-steroidal anti-inflammatory drugs (NSAIDs).* No pharmacokinetic interaction of levofloxacin with theophylline was detected. However, a significant reduction of the seizure threshold is possible when quinolones are co-administered with theophylline, NSAIDs, and other agents that reduce the seizure threshold. Levofloxacin concentrations while taking fenbufen were about 13% higher compared to levofloxacin alone.

*Systemic corticosteroids (for example, prednisone).* Concomitant use with corticosteroids may increase the risk of tendinitis and tendon rupture.

Tendon rupture may occur both after the start of therapy and within a few months after its completion (see the section "Special warnings and precautions for use").

*Probenecid and cimetidine.* Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin decreases in the presence of cimetidine by 24 % and probenecid by 34 %. This is due to the fact that both drugs are able to block the renal tubular secretion of levofloxacin. Levofloxacin should be used with caution concomitantly with drugs that affect the tubular renal secretion, such as probenecid and cimetidine, especially in patients with renal insufficiency.

*Other information.* Concomitant use with the following drugs: calcium carbonate, digoxin, glibenclamide, ranitidine has no clinically significant effect on levofloxacin pharmacokinetics.

#### **The effect of levofloxacin on other medicinal products.**

*Cyclosporin.* The half-life of cyclosporine was increased by 33 % when co-administered with levofloxacin.

*Vitamin K antagonists.* When used concomitantly with vitamin K antagonists (for example, warfarin), increased coagulation test parameters (prothrombin time/international normalized ratio), and/or bleeding, which may be severe, have been reported. In view of this, patients concomitantly using vitamin K antagonists should monitor coagulation parameters (see section "Special warnings and precautions for use").

*Drugs known to prolong the QT interval.* Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving medicinal products known to prolong QT interval (e.g., Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

*Theophylline.* Levofloxacin does not affect the pharmacokinetics of theophylline (CYP1A2 substrate), which indicates that levofloxacin is not a CYP1A2 inhibitor.

#### **Other forms of interaction.**

*Food intake.* No clinically significant food interactions were observed. Thus, tablets can be taken regardless of meal.

It is not recommended to drink alcohol during levofloxacin administration.

### ***Special warnings and precautions for use.***

Administration of levofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolones or fluoroquinolones. Treatment of these patients with

levofloxacin should only be initiated in the absence of alternatives and after careful benefit/risk assessment.

*Prolonged, disabling, and potentially irreversible serious adverse reactions.* In isolated cases, patients receiving fluoroquinolones, regardless of age and available risk factors, have developed prolonged (lasting for months or years), disabling and potentially irreversible serious adverse reactions that affect different, and sometimes multiple, body systems (musculoskeletal system, nervous system, mental health and sense organs). The drug should be discontinued immediately after the first signs or symptoms of any serious adverse reaction and medical advice should be sought.

*Aortic aneurysm and dissection.* Epidemiologic studies have reported about increased risk of aortic aneurysm and dissection after administration fluoroquinolones, particularly in the elderly.

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 consult immediately a doctor in an emergency department.

*Tendinitis and tendon rupture.*

In isolated cases, patients may experience tendinitis. The development of tendinitis and tendon rupture (in particular, but not limited to the Achilles tendon), sometimes on both sides, may occur as early as within first 48 hours after starting treatment with quinolones or fluoroquinolones, and such cases have been reported to occur even several months after drug discontinuation. The risk of tendinitis development and tendon rupture is increased in elderly patients, patients with impaired renal function, patients who have undergone parenchymal organ transplantation, patients receiving a daily dose of 1000 mg of levofloxacin, as well as in patients who are concomitantly receiving corticosteroid treatment. Accordingly, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (for example, painful swelling, inflammation), the treatment with levofloxacin should be discontinued immediately and alternative treatment options should be considered. The affected limbs should be treated accordingly (for example, by immobilizing the tendon). If there are signs of tendinopathy, it is not recommended to use corticosteroids.

*Myasthenia gravis.* Fluoroquinolones, including levofloxacin, block neuromuscular transmission and may induce muscle weakness in patients with *myasthenia gravis*. Postmarketing serious adverse reactions, including deaths and the requirement for respiratory support, have been reported in patients with *myasthenia gravis*, treated with fluoroquinolones. Levofloxacin is not recommended for use in patients with a history of *myasthenia gravis*.

*Peripheral neuropathy.* Cases of sensory and sensorimotor peripheral neuropathy resulting in paresthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Levofloxacin should be discontinued if the patient experiences symptoms of neuropathy, such as pain, burning, tingling, numbness, or weakness, to prevent the development of a potentially irreversible condition.

*Patients predisposed to seizures.* Quinolones may lower the seizure threshold and trigger seizures. Levofloxacin is contraindicated in patients with a history of epilepsy, additionally (like other quinolones) it should be used with extreme caution in patients prone to seizures, and patients with existing central nervous system (CNS) lesions, with concomitant therapy with fenbufen and similar NSAIDs or drugs that increase convulsive readiness (lower the seizure threshold), such as theophylline (see section "Interactions with other drugs and other types of interactions"). In case of seizures, treatment with levofloxacin should be discontinued.

*QT interval prolongation.* QT interval prolongation has been reported with fluoroquinolones. Caution should be taken when using fluoroquinolones, including levofloxacin, in patients with known risk factors for prolongation of the QT interval such as:

- congenital or acquired 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 (in particular, hypokalemia, hypomagnesemia);
- cardiac disease (e.g., heart failure, myocardial infarction, bradycardia).

Elderly patients and women are more sensitive to QT-prolonging drugs. In this regard, it is necessary to use fluoroquinolones, in particular levofloxacin, with caution in patients of these subgroups.

*Hypersensitivity reactions.* Levofloxacin can cause serious, potentially fatal hypersensitivity reactions (e.g., angioedema, anaphylactic shock), even following the initial dose. In this case, patients should stop treatment and immediately consult a physician.

*Severe bullous reactions.* Severe bullous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis (also known as Lyell's syndrome), and drug-induced rashes with eosinophilia and systemic symptoms (DRESS syndrome) have been reported with levofloxacin. When prescribing the drug, patients should be warned about the signs and symptoms of severe skin reactions and be carefully monitored. If signs and symptoms suggestive of these reactions appear, levofloxacin should be discontinued immediately and alternative treatment should be considered. If a patient has a history of serious reactions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, or DRESS syndrome, repeated prescription of levofloxacin to this patient is prohibited.

*Superinfection.* The use of levofloxacin, especially over a long time, may result in the 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 test results by more specific methods.

Levofloxacin inhibits the growth of *Mycobacterium tuberculosis* and, therefore, a false-negative result may be observed during a bacteriological study in patients with tuberculosis.

*Methicillin-resistant Staphylococcus aureus (MRSA)* is resistant to fluoroquinolones, in particular to levofloxacin, so levofloxacin is not recommended for the treatment of known or suspected MRSA infections, except in cases where the results of laboratory tests confirmed susceptibility of the pathogen to levofloxacin.

Levofloxacin-resistant *E. coli* may be a common causative agent of urinary tract infections, which should be taken into account when prescribing levofloxacin to patients with urinary tract diseases. Physicians who prescribe therapy are advised to consider the local prevalence of *E. coli* resistance to fluoroquinolones.

Levofloxacin can be used in the treatment of acute bacterial sinusitis and exacerbation of chronic bronchitis when these infections have been adequately diagnosed. Hospital-acquired infections caused by *Pseudomonas aeruginosa* may require combination therapy.

*Clostridium difficile-associated diseases.* Diarrhea, especially severe, persistent and/or hemorrhagic, during or after treatment with levofloxacin, including several weeks after use, may be symptomatic of a disease caused by *Clostridium difficile*, the most severe form of which is pseudomembranous colitis. If pseudomembranous colitis is suspected, levofloxacin should be discontinued immediately and appropriate therapy should be initiated immediately, including specific therapy (for example, oral administration of vancomycin). Medicinal products inhibiting the peristalsis are contraindicated in this clinical setting.

*Inhalation anthrax.* Clinical practice is based on *in vitro* *Bacillus anthracis* susceptibility data, as well as on animal experimental data together with limited human data. Physicians should refer to national and/or international guidelines regarding the treatment of anthrax.

*Changes in blood glucose levels.* As with other quinolones, changes in blood glucose levels are possible, including both hyperglycemia and hypoglycemia, especially in diabetic patients who concomitantly use oral hypoglycemic agents (glibenclamide) or insulin. Cases of hypoglycemic coma have been reported. In patients with diabetes mellitus, it is recommended to monitor blood glucose level.

*Photosensitivity reactions.* Cases of photosensitivity have been reported with levofloxacin. In order to prevent the occurrence of photosensitivity reactions, patients taking levofloxacin are advised to avoid strong sunlight or artificial ultraviolet radiation (for example, artificial UV lamps, tanning beds) during treatment or within 48 hours after discontinuation of the drug.

*Patients treated with vitamin K antagonists.* Due to a possible increase in the parameters of coagulation tests (prothrombin time/international normalized ratio) and/or an increase in the frequency of hemorrhagic complications in patients taking Leflock in combination with a vitamin K antagonist (for example, warfarin), coagulation tests should be monitored when these drugs are used concomitantly (see section "Interactions with other drugs and other types of interactions").

*Psychotic reactions.* Psychotic reactions have been reported in patients taking quinolones, including levofloxacin. In very rare cases, these have progressed to suicidal ideation and self-destructive behaviour, sometimes after only a single dose of levofloxacin. If the patient develops these reactions, levofloxacin should be discontinued and appropriate measures initiated. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with a history of psychiatric diseases.

*Patients with glucose-6-phosphate dehydrogenase deficiency.* In patients with latent or detected glucose-6-phosphate dehydrogenase deficiency, the use of antibacterial agents of the quinolone group may lead to hemolytic reactions, so levofloxacin should be used with caution, monitoring the patient's condition regarding the possible occurrence of hemolysis.

*Patients with renal impairment.* Since levofloxacin is mainly excreted by the kidneys, dose adjustment is necessary for patients with impaired renal function (renal failure) (see section "Posology and method of administration").

*Hepatobiliary disorders.* Cases of necrotic hepatitis, up to life-threatening liver failure, have been reported with levofloxacin, mainly in patients with severe underlying diseases, such as sepsis. Patients should be advised to stop treatment and contact their physician if symptoms of hepatic disease such as anorexia, jaundice, black urine, pruritus, or tender abdomen, develop.

*Vision disorders.* If vision disorders or any effects on the eyes are observed, an eye specialist should be consulted immediately.

*Relevant information on excipients.* The composition of the drug includes dye "Yellow sunset FCF" (E 110), which can cause allergic reactions.

*Fertility, pregnancy and lactation.* Due to the possibility of damage to the articular cartilage in the growing organism by quinolones, the drug is contraindicated for use in pregnant and breast-feeding women.

If pregnancy is diagnosed during the use of the drug, the physician should be informed about this. Levofloxacin causes no impairment of fertility or reproductive performance in animals.

*Effects on ability to drive and use machines.*

Such nervous system adverse reactions as dizziness, drowsiness, visual and hearing disorders disrupt the ability to concentrate and react quickly, so the drug should be used with caution in patients who drive vehicles or work with mechanisms that require increased attention.

### ***Posology and method of administration.***

The drug should be taken 1 or 2 times a day, regardless of food intake. Tablets should be swallowed without chewing and with sufficient amount of liquid.

The dose depends on the type, severity of the infection, and sensitivity of the likely pathogen. The drug can be used to complete the course of therapy in patients who have shown improvement in the initial administration of levofloxacin; taking into account the bioequivalence of parenteral and oral forms, the same dosage can be used.

It is recommended to continue treatment with levofloxacin for 48-72 hours after normalization of body temperature or the absence of pathogens confirmed by microbiological tests.

Levofloxacin should be taken at least 2 hours before or 2 hours after taking medications containing iron salts, antacids, and sucralfate, as the latter may reduce the absorption of the drug.

Dosage in adult patients with normal renal function with creatinine clearance >50 ml/min is given in Table 3.

Table 3

Therapeutic indication	Daily dose	Quantity of administrations per day	Duration of treatment
Acute bacterial sinusitis	500 mg	Once a day	10–14 days
Exacerbation of chronic obstructive pulmonary disease, including bronchitis	500 mg	Once a day	7–10 days
Community-acquired pneumonia	500 mg	Once or twice a day	7–14 days
Uncomplicated cystitis	250 mg	Once a day	3 days
Complicated genitourinary system infections	500 mg	Once a day	7–14 days
Acute pyelonephritis	500 mg	Once a day	7–10 days
Chronic bacterial prostatitis	500 mg	Once a day	28 days
Complicated skin and soft tissue infections	500 mg	Once or twice a day	7–14 days
Inhalation anthrax: post-exposure prophylaxis and curative treatment	500 mg	Once a day	8 weeks

Since levofloxacin is primarily excreted by the kidneys, the dose should be reduced in patients with impaired renal function. Dosage in adult patients with renal impairment with creatinine clearance <50 ml/min is given in Table 4.

Table 4

Creatinine clearance (mL/min)	Dosage regimen (depending on the severity of the infection and disease entity)		
	250 mg/24 h	500 mg/24 h	500 mg/12 h
	first dose: 250 mg	first dose: 500 mg	first dose: 500 mg
50–20	subsequent: 125 mg/24 h	subsequent: 250 mg/24 h	subsequent: 250 mg/12 h
19–10	subsequent: 125 mg/48 h	subsequent: 125 mg/24 h	subsequent: 125 mg/12 h
< 10 (as well as in hemodialysis and CAPD <sup>1</sup> )	subsequent: 125 mg/48 h	subsequent: 125 mg/24 h	subsequent: 125 mg/24 h

<sup>1</sup> No additional doses are required after hemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

*Dosage for patients with hepatic impairment.*

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

*Dosage for elderly.*

No adjustment of dose is required if there is no hepatic impairment.

*Children.*

The drug is contraindicated in children, since damage to articular cartilage is not excluded.

**Overdose.**

According to the results of studies on the toxicity of the drug in animals or clinical pharmacology studies performed with supra-therapeutic doses, the most important signs to be expected after an



acute overdose of levofloxacin are central nervous system symptoms such as confusion, dizziness, impaired consciousness, and convulsive seizure, as well as prolongation of the QT interval and gastrointestinal reactions, such as mucosal erosions. During post-marketing period experience in such cases CNS effects have been observed, such as confusion, convulsions, hallucinations and tremor.

In case of overdose, the patient should be closely monitored, including ECG. Treatment is symptomatic. Antacids can be used to protect the gastric mucosa. Hemodialysis, including peritoneal dialysis and continuous ambulatory peritoneal dialysis (CAPD), are not effective in eliminating levofloxacin. No specific antidote is known.

### ***Undesirable effects.***

All undesirable effects are listed by system organ class and frequency: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ), unknown (cannot be estimated from the available data).

*Eye disorders\**: rarely – vision disorders, including blurred vision; frequency unknown – transient vision impairment, temporary vision loss, uveitis.

*Ear and labyrinth disorders\**: uncommon: vertigo; rare: tinnitus; unknown: impaired hearing, hearing loss.

*Respiratory, thoracic and mediastinal disorders*: uncommon – dyspnea; unknown – bronchospasm, allergic pneumonitis.

*Gastrointestinal disorders*: common – diarrhea, vomiting, nausea; uncommon – abdominal pain, dyspepsia, flatulence, constipation; unknown – hemorrhagic diarrhea which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis, pancreatitis.

*Hepatobiliary disorders*: common – elevated hepatic enzymes (alanine aminotransferase (ALT)/aspartate aminotransferase (AST), alkaline phosphatase, gamma-glutamyltranspeptidase (GGT)); uncommon – increased blood bilirubin; frequency unknown – hepatitis, jaundice and severe liver dysfunction, including cases of acute liver failure, sometimes fatal, mainly in patients with severe underlying diseases.

*Renal and urinary disorders*: uncommon – elevated serum creatinine; unknown frequency – acute renal failure (e.g., due to interstitial nephritis).

*Endocrine system disorders*: rare – syndrome of inappropriate antidiuretic hormone secretion (SIADHS).

*Metabolism and nutrition disorders*: uncommon – anorexia; rare – hypoglycemia, especially in patients with diabetes mellitus, hypoglycemic coma; frequency unknown – hyperglycemia, as with the use of other fluoroquinolones, porphyria attacks are possible in patients with porphyria.

*Nervous system disorders\**: common – dizziness, headache; uncommon – somnolence, tremor, dysgeusia, including ageusia (loss of taste); rare – convulsions, paresthesia, memory loss; frequency unknown – sensory or sensorimotor peripheral neuropathy, parosmia, including anosmia, dyskinesia, extrapyramidal disorders, syncope, benign intracranial hypertension.

*Psychiatric disorders\**: common – insomnia; uncommon – anxiety, confusion, nervousness; rare – depression, agitation, nightmares, abnormal dreams; frequency unknown – psychotic reactions, including hallucinations, paranoia, self-destructive behavior, suicidal orientation of thinking or actions.

*Cardiovascular system disorders*: common – phlebitis; rare – tachycardia; palpitations, hypotension; frequency unknown – ventricular tachycardia, which may lead to cardiac arrest; ventricular arrhythmia; *torsade de pointes* arrhythmia, which may lead to cardiac arrest (mainly in patients with risk factors for prolongation of the QT interval); prolongation of the QT interval on an electrocardiogram, allergic vasculitis.

*Blood and lymphatic system disorders*: uncommon – leukopenia, eosinophilia; rare – thrombocytopenia, neutropenia; frequency unknown – agranulocytosis, pancytopenia, hemolytic anemia.

*Immune system disorders:* rare – hypersensitivity reactions, angioedema; frequency unknown – anaphylactic and anaphylactoid shock (anaphylactic and anaphylactoid reactions may sometimes occur after taking the first dose).

*Skin and subcutaneous tissue diseases:* uncommon – rashes, pruritus, skin redness, urticaria, hyperhidrosis; rare – drug rashes with eosinophilia and systemic symptoms (DRESS-syndrome), local drug rashes; frequency unknown – hypersensitivity to solar and ultraviolet radiation, toxic epidermal necrolysis (Lyell's syndrome), Stevens-Johnson syndrome, exudative erythema multiforme, leukocytoclastic vasculitis, stomatitis. Skin and mucosal reactions may sometimes occur even after taking the first dose.

*Musculoskeletal system and connective tissue disorders\*:* uncommon – arthralgia, myalgia; rare – tendon damage, including tendinitis, muscle weakness, which may be of particular importance for patients with severe myasthenia gravis; frequency unknown – rhabdomyolysis, tendon (may occur within 48 hours from the start of treatment and affect the Achilles tendon of both legs), ligament, muscle rupture, arthritis.

*General disorders\*:* uncommon – asthenia; rare – pyrexia; frequency unknown – general weakness, pain (including back, chest and limb pain).

*Infections and infestations:* uncommon – fungal infections, including *Candida* fungi (and proliferation of other resistant microorganisms), development of secondary infections.

Other undesirable side effects associated with administration of fluoroquinolones – include porphyria attacks in patients with porphyria.

\* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious adverse reactions affecting several, sometimes multiple, body systems and sense organs (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathy associated with paresthesia, depression, fatigue, memory impairment, sleep disorders, hearing, vision, taste and smell disorders) have been associated with the use of quinolones and fluoroquinolones, irrespective of pre-existing risk factors.

#### Reporting of suspected adverse reactions.

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

**Shelf life.** 250 mg film-coated tablets – 2 years.

500 mg film-coated tablets – 3 years.

**Special precautions for storage.** Store in the original package at temperature not above 25 °C. Keep out of reach of children.

Nature and contents of container. 5 tablets in a blister; 1 blister in carton box.  
10 tablets in a blister; 10 blister in a carton box.

#### **Category of release.**

Prescription only medicine.

#### **Manufacturer.**

PrJSC "Pharmaceutical Firm "Darnitsa".

#### **The manufacturer's location and address of the place of business.**

13, Boryspilska Street, Kyiv, 02093, Ukraine.

**Date of last revision.** 15.10.2020.