SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS

● Fluoroquinolones, including LEVOXIPOLIN, have been associated with disabling and potentially irreversible serious adverse reactions including:
- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects

Discontinue LEVOXIPOLIN immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.

● Fluoroquinolones, including LEVOXIPOLIN, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid LEVOXIPOLIN in patients with a known history of myasthenia gravis.

1. NAME OF THE MEDICINAL PRODUCT

LEVOXIPOLIN 500 mg/100 ml Solution for I.V. Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Substance:
100 ml of solution for infusion contains,
Levofloxacin 500 mg (equivalent to 512.48 mg of levofloxacin hemihydrate)

Excipient(s):
Sodium chloride 900 mg
Sodium hydroxide (pH=4.8)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Greenish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

LEVOXIPOLIN is indicated for the treatment of following infections in adults which are caused by levofloxacin-susceptible microorganisms:

- Community acquired pneumonia

Due to *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains with MIC value ≥ 2 μg/ml for penicillin), *Haemophilus influenzae, Haemophilus parainfluenzae, Klebsiella pneumoniae, Moraxella catarrhalis, Chlamydia pneumoniae, Legionella pneumophila* or *Mycoplasma pneumoniae.*

- Complicated Urinary Tract Infections including pyelonephritis

Acute pyelonephritis caused by *Escherichia coli;* caused by *Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis* or *Pseudomonas aeruginosa.*

- Prostatitis

Caused by *Escherichia coli, Enterococcus faecalis* or *Staphylococcus epidermidis.*

- Skin and soft tissue infections

Skin and skin structure infections due to methicillin-susceptible *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes* or *Proteus mirabilis* and uncomplicated skin and skin structure infections including abscesses, cellulitis, furuncles, impetigo, pyoderma, wound infections, due to methicillin-susceptible *Staphylococcus aureus*, or *Streptococcus pyogenes*.

- Hospital acquired pneumonia

Caused by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Escherichia coli*, *Klebsiella pneumoniae*, *Enterobacter aerogenes Haemophilus influenza* or *Streptococcus pneumoniae* apart from methicillin resistance staphylococci. Where *Pseudomonas aeruginosa* is a documented or presumptive pathogen, combination therapy with an anti-pseudomonal β-lactam is recommended.

- Inhalation Anthrax

Prophylaxis and curative treatment following exposure to aerosolized *Bacillus anthracis*.
Consideration should be given to official national guidance on the appropriate use of antibacterial agents and local susceptibility of pathogens (see section 4.4).

4.2 Posology and method of administration

LEVOXIPOLIN solution for infusion may be administered by slow infusion (infusion for at least 600 minutes) once or twice daily. The dosage depends on the type and severity of the infection and the susceptibility of the active pathogen. Switching to oral administration several days after initial IV administration may be possible depending on patient's condition. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology:
In adults, following dose recommendations can be given for LEVOXIPOLIN:

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

Indication	**Daily dosage** (according to severity of infection)	**Duration of use** (according to severity of infection)
Community-acquired pneumonia	500 mg once or twice daily	7-14 days
Pyelonephritis	500 mg once daily*	7-10 days
Complicated urinary tract infections	500 mg once daily	7-14 days
Prostatitis	500 mg once daily	28 days
Skin and soft tissue	250 mg once daily or 500 mg once	7-14 days

infections	or twice daily	
Hospital acquired pneumonia	750 mg once daily	10-14 days
Inhalation arthrax	500 mg once daily	8 weeks

**Dose increase should be considered in cases of severe infection.*

Method of administration:
LEVOXIPOLIN solution for infusion is only intended for slow intravenous infusion. It is administered once or twice daily. The infusion time must be 60 minutes for 500 mg LEVOXIPOLIN solution for infusion (see section 4.4.). Switching to oral administration at the same dosage several days after initial IV administration may be possible depending on patient's condition.

For incompatibilities see 6.2.

Duration of treatment
Treatment duration depends on the course of the illness (see above table). As with all antibiotic treatments in general, the use of LEVOXIPOLIN should be continued for at least 48-72 hours after the patient fever has dropped and evidence of bacterial eradication has been obtained.

Special populations:

Renal failure:
Use as indicated in the table below.
Dosage in patients with a creatinine clearance ≤ 50 ml/min (According to severity of inspection).

	250 mg/24 h	**500 mg/24 h**	**500 mg/12 h**
Creatinine clearance	**First dose 250 mg**	**First dose 500 mg**	**First dose 500 mg**
	then:	*then:*	*then:*
50-20 ml/min	125 mg/24 h	250 mg/24 h	250 mg/12 h
	then:	*then:*	*then:*
19-10 ml/min	125 mg/48 h	125 mg/24 h	125 mg/12 h
<10 ml/min (including haemodialysis and continuous ambulatory peritoneal dialysis)*	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/24 h

* No additional doses are required after haemodialysis or continuous ambulatory peritoneal dialysis.

Hepatic failure:
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.

Pediatric population:
LEVOXIPOLIN is contraindicated in children and growing adolescents (see section 4.3).

Geriatric population:
No adjustment of dose is required in the elderly, other than that imposed by consideration of renal function (see section 4.4., QT interval prolongation).

4.3 Contraindications

LEVOXIPOLIN (levofloxacin) should not be used in following cases:

- In patients with known hypersensitivity to levofloxacin or to any of the ingredients of LEVOXIPOLIN solution for infusion or to any other antibacterial drug from the fluoroquinolone group.
- 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

Its use is contraindicated in children or growing adolescents, during pregnancy and in breast-feeding women based on animal studies, as the risk of damage to the developing cartilage tissue of the developing organism cannot be completely ruled out.

4.4 Special warnings and precautions for use

Serious potentially irreversible adverse reactions that cause disability, including tendonitis and tendon rupture, peripheral neuropathy, and central nervous system effects

Fluoroquinolones, including LEVOXIPOLIN, have been associated with potentially irreversible serious adverse reactions that can cause disability. Common adverse reactions include musculoskeletal and peripheral nervous system (tendinitis, tendon rupture, swelling or inflammation in tendons, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, swelling in joints) atralgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendency, insonmia, severe headache and confusion) (See Section 4.8).

These reactions can occur within hours or weeks after starting LEVOXIPOLIN. Patients of any age group or without pre-existing risk factors experienced these adverse reactions.

In the event that the first signs or symptoms of any serious adverse reaction occur, LEVOXIPOLIN should be discontinued immediately. In addition, the use of fluoroquinolones, including LEVOXIPOLIN, should be avoided in patients experiencing any of these serious adverse reactions associated with fluoroquinolones.

General warnings
The prevalence of acquired resistance may vary from country to country and from time to time for some species of bacteria. For this reason, there is a need for local data on resistance;

especially in cases of severe infections or in the case of no response to treatment, the pathogen should be isolated and microbiologically diagnosed and evidence of pathogen susceptibility should be sought.

For severe pneumococcal pneumonia cases, LEVOXIPOLIN may not be the most appropriate treatment.
Combined treatment may be needed for nosocomial infections caused by *P. aeruginosa*.

The resistance of E. Coli, the most common pathogen in urinary tract infections, to fluoroquinolones varies within the European Union. Physicians are advised to consider the local prevalence of E. Coli's resistance to fluoroquinolones when prescribing.

Methicillin-resistant *S. aureus* (MRSA):
Methicillin-resistant *S.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 if it is not appropriate to use generally recommended antibacterial agents for the treatment of MRSA infections),.

Patients predisposed to convulsions:
Quinolones can lower the seizure threshold and trigger seizures. As with other quinolones, LEVOXIPOLIN solution for infusion is contraindicated in patients with a history of epilepsy(See Section 4.3) and, as with other quinolones, should be used with extreme caution in patients who are prone to epileptic seizures or who are simultaneously treated with drugs that lower the seizure threshold, such as theophylline (See Section 4.5). In case of convulsion seizures (see section 4.8), levofloxacin treatment should be discontinued.

Clostridium difficile-associated disease (Pseudomembranous colitis)
If severe, persistent and / or bloody diarrhea occurs during or after LEVOXIPOLIN infusion solution treatment (including a few weeks after treatment), this may be a symptom of Clostridium difficile-associated pseudomembranous colitis. The severity of this disease can range from moderate to life-threatening size, the most severe being pseudomembranous colitis (see section 4.8). Therefore, it is important to consider this diagnosis in patients who develop severe diarrhea during and after treatment with levofloxacin. This is the most serious form of pseudomembranous enterocolitis. If pseudomembranous enterocolitis is suspected, LEVOXIPOLIN treatment should be terminated immediately and appropriate treatment should be started without delay. In this clinical situation, drugs that prevent bowel movements are contraindicated.

Tendonitis and tendon rupture:
Rarely, tendonitis may occur. It most commonly affects the Achilles tendon and can lead to tendon rupture. Tendonitis and tendon rupture (sometimes bilateral) can occur within 48 hours of starting treatment; Cases of tendonitis and tendon rupture have been reported up to several months after the end of treatment. The risk of tendonitis and tendon rupture increases in the

elderly, patients using corticosteroids and those who take 1000 mg daily dose. Also, caution is recommended when using fluoroquinolones in this population, as transplanted patients are at increased risk of tendonitis. In elderly patients, the daily dose should be adjusted according to creatinine clearance (see section 4.2). These patients LEFOX İ.V. If prescribed, they need to be followed closely. All patients who experience symptoms of tendonitis should inform their doctor. If tendinitis is suspected, LEFOX İ.V. treatment should be discontinued immediately and appropriate treatment should be initiated in the form of immobilization of the affected tendon (see sections 4.3 and 4.8).

Hypersensitivity reactions:
Levofloxacin, rarely even after the first dose, can cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema up to anaphylactic shock), occasionally following the initial dose (see section 4.8). Patients should discontinue treatment immediately and contact their physician or an emergency physician

Severe bullous reactions:
Cases of severe bullous skin reactions, such as Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported with Levofloxacin (see section 4.8). Patients should be advised to contact their doctor immediately prior to continuing treatment if skin and/or mucosal reactions occur.

Hepatobiliary disorders:
Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin, in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

QT interval prolongation:
Very rare cases of prolongation of the QT interval have been reported in patients receiving fluoroquinolones including levofloxacin.
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:

- Uncorrected electrolyte imbalance (e.g. hypokalemia, hypomagnesemia)
- Congenital long QT syndrome
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including levofloxacin, in these populations (See Sections 4.2, 4.5, 4.8 and 4.9).

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 simultaneous with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

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. Fluoroquinolone is not recommended in patients with a known history of myasthenia gravis.

Patients with renal impairment:
Since levofloxacin is excreted mainly by the kidneys, the dose of LEVOXIPOLIN should be adjusted in patients with renal impairment (see section 4.2).

Photosensitisation:
Cases of photosensitization due to levofloxacin have been reported (see section 4.8). It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays such as solarium during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Superinfection:
As with other antibiotics, the prolonged use of levofloxacin may result in overgrowth of non-susceptible organisms. Repetitive assessments of the patient's condition are important. If superinfection occurs during therapy, appropriate measures should be taken.

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 is to be used in such patients, the potential for hemolysis should be closely monitored.

Peripheral neuropathy:
Peripheral sensory neuropathy and peripheral sensory motor 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.

Inhalation Anthrax:
Use in humans is based on in vitro Bacillus anthracis susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Infusion Time:
The recommended infusion time for LEVOXIPOLIN 500 mg/100 ml solution for I.V. infusion is at least 60 minutes. Patient should be observed during this time. Tachycardia and a temporary decrease in blood pressure may develop and in rare cases, as a consequence of a profound drop in blood pressure, circulatory collapse may occur with LEVOXIPOLIN I.V. infusion. Should a conspicuous drop in blood pressure occur during infusion of levofloxacin, (l-isomer of ofloxacin) the infusion must be halted immediately.

Patients treated with Vitamin K antagonists:
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin), coagulation tests should be monitored when these drugs are given concomitantly (see section 4.5).

Psychotic reactions:
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour-sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if levofloxacin is to be used in psychotic patients or in patients with history of psychiatric disease.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see sections 4.7 and 4.8).

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

Aortic aneurysm and dissection:
Epidemiological studies report an increased risk of aortic aneurysm and dissection, especially in the elderly population after the use of fluoroquinolone.

Therefore, fluoroquinolones are found in patients with a positive family history of aneurysm disease, patients with previous aortic aneurysm and / or aortic dissection, patients with other risk factors for aortic aneurysm and dissection, or predisposing conditions (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis) should only be used after careful benefit / risk assessment and other therapeutic options.

In the event of sudden abdominal, chest or back pain, patients should be advised to contact the emergency room immediately.

Sodium content

This medicinal product contains 15.4 mmol (354 mg) of sodium per 100 ml dose. This should be considered for patients in the controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Theophylline, fenbufen or similar non-steroidal anti-inflammatory drugs
No pharmacokinetic interactions of levofloxacin were found with theophylline in a clinical study. However a pronounced lowering of the cerebral seizure threshold may occur when quinolones are given concurrently with theophylline, non-steroidal anti-inflammatory drugs, or other agents which lower the seizure threshold.

Levofloxacin concentrations were about 13% higher in the presence of fenbufen than when administered alone.

Probenecid and cimetidine
Caution should be exercised when levofloxacin is coadministered with drugs that effect the tubular renal secretion such as probenecid and cimetidine, especially in renally impaired patients.

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was reduced by cimetidine at 24% and probenecid at 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.

Ciclosporin
The half-life of ciclosporin was increased by 33% when coadministered with levofloxacin.

Vitamin K antagonists
Increased coagulation tests (PT/INR) and/or bleeding, which may be severe, have been reported in patients treated with levofloxacin in combination with a vitamin K antagonist (e.g. warfarin). Coagulation tests, therefore, should be monitored in patients treated with vitamin K antagonists.
Patients should also be monitored carefully for signs of bleeding (See Section 4.4).

Drugs known to prolong QT interval
Levofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics). (see section 4.4 QT interval prolongation).

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, digioxin, glibenclamide, ranitidine.

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

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C
No adequate data is available on the use of levofloxacin in pregnant women.

Women with childbearing potential /Contraception
No adequate data is available on the use of levofloxacin in women with childbearing potential.

Pregnancy
There are insufficient data on the use of levofloxacin in pregnant women. Levofloxacin is contraindicated during pregnancy.

Studies on animals are insufficient in terms of the effects on pregnancy and / or embryonal / fetal development and / or birth / postnatal development. (See sections 4.3 and 5.3). The potential risk for humans is unknown. 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, LEVOXIPOLIN solution for infusion must not be used during pregnancy.

Lactation
Levofloxacin is contraindicated during breastfeeding. There is insufficient/limited evidence on the excretion of Levofloxacin in human and animal milk. The risk for the breastfed child cannot be ruled due to physicochemical and available pharmacodynamic/toxicological data for the excretion of levofloxacin by 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, LEVOXIPOLIN solution for infusion must not be used during breastfeeding (see sections 4.3 and 5.3).

Reproduction/Fertility
No adequate data is available on the effect of Levofloxacin on reproduction ability in human.

4.7 Effects on ability to drive and use machines
Use of LEVOXIPOLIN may cause some undesirable effects such as dizziness/vertigo, visual disturbances, drowsiness that may impair the patient’s ability to concentrate and react. Reduced ability may constitute a risk in situations where these abilities are of special

importance e.g. driving a car or operating machinery. When using LEVOXIPOLIN, patients experiencing these side effects should not drive and use machinery.

4.8 Undesirable effects

The information given below is based on data from clinical studies in more than 8300 patients and on extensive post marketing experience. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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 infections, including candida infection, pathogen resistance

Blood and the lymphatic system disorders

Uncommon: Leukopenia, eosinophilia

Rare: Neutropenia, trombocytopenia

Not known (Post-marketing data): Pancytopenia, agranulocytosis, haemolytic anemia

Immune system disorders

Rare: Angiodema, hypersensitivity

Not known (Post-marketing datai): Anaphylactic shock and Anaphylactoidashock.

Anaphylactic and anaphalactoid reactions may sometimes occur, even after the first dose (see section 4.4).

Metabolism and nutrition disorders

Uncommon: Anorexia

Rare: Hypoglycaemia particularly in diabetic patients (see section 4.4)

Not known: Hyperglycaemia, Hypoglycaemic coma (see section 4.4)

Psychiatric disorders

Common: Insomnia

Uncommon: Anxiety, Confusional state, nervousness

Rare: Psychotic reactions (with eg hallucination, paranoia), depression, agitation, abnormal dreams, nightmares

Not known (Post-marketing data): Psychotic with self-endangering behaviour including suicidal ideation or suicide attempt

Nervous system disorders

Common: Headache, dizziness

Uncommon: Somnolence, tremor, dysgeusia

Rare: Paraesthesia, convulsions (see section 4.4),

Not known (Post-marketing data): Peripheral sensory neuropathy (see section 4.4), peripheral sensory motor neuropathy (see section 4.4), parosmia including anosmia, dyskinesia, extrapyramidal disorder, ageusia, syncope, benign intracranial hypertension

Eye disorders
Rare: Visual disturbances such as blurred vision
Not known: Transient vision loss (see section 4.4)

Ear and Labyrinth disorders
Uncommon: Vertigo
Rare: Tinnitus
Not known: Hearing impaired, hearing loss

Cardiac disorders
Rare: Tachycardia, palpitation
Not known (Post-marketing data): Ventricular arrhythmia and Torsade de Pointes, Ventricular tachycardia, which may result in cardiac arrest, electrocardiogram QT prolonged (see section 4.4, QT prolongation and section 4.9).

Vascular disorders
Common: Phlebitis
Rare: Hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Dispnoea
Not known (Post-marketing data): Bronchospasm, pneumonitis allergic

Gastrointestinal disorders
Common: Diarrhoea, vomiting, nausea
Uncommon: Abdominal pain, Dyspepsia, Flatulence, Constipation
Not known (Post-marketing data): Diarrhoea – haemorrhagic which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), Pancreatitis

Hepatobiliary disorders
Common: Elevated hepatic enzymes (ALT/AST, alkaline phosphatase, GGT)
Uncommon: Blood bilirubin increased
Not known (Post-marketing data): Sever liver injury, jaundice
Reports of fatal cases with acute liver failure, primarily in patients with severe underlying diseases (see section 4.4), hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Pruritis, rash, urticaria, hyperhydrosis

Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Photosensitivity reaction (see section 4.4), Leukocytoclastic vasculitis, Stomatitis.
Mucocutaneous reactions may sometimes occur even after the first dose.

Musculoskeletal and connective tissue disorders
Uncommon: Athralgia, myalgia
Rare: Muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4 Exacerbation of Myasthenia Gravis)
Not known (Post-marketing data): Rhabdomyolysis tendon rupture (eg Achilles tendon) (See Section 4.4), ligament rupture, muscle rupture, arthritis

Renal and urinary tract disorders
Uncommon: Blood creatinine increased
Rare: Acute renal failure (e.g. due to interstitial nephritis)

General disorders and administration site conditions
Common: Infusion site reaction (pain, reddening)
Uncommon: Asthenia
Rare: Fever
Not known: Pain (back, chest and extremities)

Other undesirable effects which have been associated with fluoroquinolone administration
Very rare: attacks of porphyria in patients with porphyria

Reporting of suspected adverse reactions
Reporting any suspected adverse reactions of drugs is very important after the authorization. Reporting enables tracking the benefit/risk balance of the medicinal product. Health professionals should report any suspected adverse reaction to Turkish Pharmacovigilance Center (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; phone: 0 800 314 00 08; fax: 0312 218 35 99).

4.9 Overdose and therapy

Signs:
According to toxicity studies in animals, the most important signs to be expected following acute overdosage of levofloxacin infusion solution are confusion, dizziness, impairment of consciousness, and convulsive seizures. Central nervous system effects including confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience. The reactions to the gastrointestinal system are nausea and mucosal erosions.

Clinical pharmacology studies with supra-therapeutic doses showed prolonged QT interval.

Treatment:

In the event of overdose, patient should be closely monitored, ECG monitoring should be undertaken, because of the possibility of QT interval prolongation and symptomatic treatment should be implemented. Antiacids may be used to protect gastric mucosa.
Haemodialysis, including peritoneal dialysis and continuous ambulatory peritoneal dialysis, are not effective in removing levofloxacin from the body. No specific antidote exists.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Parmacotherapeutic group: Quinolone antibacterials, fluoroquinolones
ATC Code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class. It 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.

Antibacterial spectrum
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.
In vitro, levofloxacin has been shown to be active on the following pathogens:

The information below reflects the European harmonization data as of August 2012.

Generally sensitive species
Aerobic Gram-positive bacteria
Bacillus anthracis
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus saprophyticus
Group C and G streptococci
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes
Aerobic Gram-negative bacteria
Eikenella corrodens
Haemophilus influenzae
Haemophilus parainfluenzae
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 where developing resistance can be a problem
Aerobic Gram-positive bacteria
Enterococcus faecalis
Staphylococcus aureus (methicillin-resistant)+
Coagulase-negative *Staphylococcus* spp.
Aerobic Gram-negative bacteria
Enterobacter 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
Naturally resistant strains
Aerobic Gram-positive bacteria
Enterococcus faecium

+ Methicillin-resistant S. aureus is also likely to exhibit equivalent resistance to fluoroquinolones, including levofloxacin.

Resistance

Resistance to levofloxacin is acquired through a stepwise process by target site mutations in both type II topoisomerases, DNA gyrase and topoisomerase IV. Other resistance mechanisms such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may also affect susceptibility to levofloxacin.

Cross-resistance between levofloxacin and other fluoroquinolones is observed. Due to the mechanism of action, there is generally no cross-resistance between levofloxacin and other classes of antibacterial agents.

Breakpoints
The EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/L).
EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriacae	≤1 mg/l	>2 mg/l
Pseudomonas spp.	≤1 mg/l	>2 mg/l
Acinetobacter spp.	≤1 mg/l	>2 mg/l
Staphylococcus spp.	≤1 mg/l	>2 mg/l
S. pneumoniae [1]	≤2 mg/l	>2 mg/l
Streptococcus A,B,C,G	≤1 mg/l	>2 mg/l
H. influenzae [2,3]	≤1 mg/l	>1 mg/l
M. catarrhalis [3]	≤1 mg/l	>1 mg/l
Non-species related breakpoints[4]	≤1 mg/l	>2 mg/l
1. The breakpoints for levofloxacin relate to high dose therapy 2. Low-level fluoroquinolone resistance (ciprofloxacin MICs of 0.12-0.5 mg/l) may occur but there is no evidence that this resistance is of clinical importance in respiratory tract infections with H. influenzae. 3. Strains with MIC values above the susceptible breakpoint are very rare or not yet reported. The identification and antimicrobial susceptibility tests on any such isolate must be repeated and if the result is confirmed the isolate must be sent to a reference laboratory. Until there is evidence regarding clinical response for confirmed isolates with MIC above the current resistant breakpoint they should be reported resistant 4. Breakpoints apply to an oral dose of 500 mg x 1 to 500 mg x 2 and an intravenous dose of 500 mg x 1 to 500 mg x 2.		

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable

5.2 Pharmacokinetic properties

General properties:

Absoprtion:
Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1-2 h (C_{max}: 5.2+/-1.2 mcg/ml following the

administration of single dose of 500 mg levofloxacin). The absolute bioavailability is 99-100 %. Levofloxacin obeys linear pharmacokinetics over a range of 50 to 1000 mg.
Steady state conditions are reached within 48 hours following a 500 mg once or twice daily dosage regimen.

The table below shows the peak and trough plasma concentrations at day 10 of multiple oral or IV 500 mg dosing administered once or twice daily:

PK Parameter (mean ±SD)	500 mg multiple-dose			
	Once daily		Twice daily	
	500 mg oral	500 mg IV*	500 mg oral	500 mg IV
Peak plasma concentration (mcg/ml)	5.7 ± 1.4	6.4 ± 0.8	7.8 ± 1.1	7.9 ± 1.1
Through plasma concentration (mcg/ml)	0.5 ± 0.2	0.6 ± 0.2	3.0 ± 0.9	2.3 ± 0.5

*Duration of 500 mg IV infusion is 60 minutes.
Food has little effect on the absorption of levofloxacin

Distribution:
The mean volume of distribution of levofloxacin is approximately 100 l after single and repeated 500 mg or 750 mg doses, indicating widespread distribution into body tissues. Approximately 30-40% of levofloxacin is bound to serum protein.

Penetration into tissues and body fluids:
Penetration into bronchial mucosa, epithelial lining fluid and alveolar macrophages
Maximum levofloxacin concentrations in bronchial mucosa and epithelial lining fluid after single administration of 500 mg p.o. were 8.3 microgram/ml and 10.9 microgram/ml respectively and serum penetration rate from th mucosa and epithelial mucosa are 1.1-1.8 and 0.8-3 respectively. These were reached respectively approximately 1 and 4 hour after administration.

The mean concentrations in the epithelial lining fluid following oral administration of 500 mg and 750 mg for 5 days and 4 hours after the last administration are 9.94 microgram/ml and 22.12 mcg/ml, respectively. In alveolar macrophages, concentrations are 97.9 mcg/ml and 105.1 mcg/ml, respectively.

Penetration into Lung Tissue
Maximum levofloxacin concentrations in lung tissue after 500 mg p.o. were approximately 11.3 μg/g and were reached between 4 and 6 hours after administration. Distribution rate from lung tissue into the plasma is 2-5.

Penetration into Blister Fluid
Maximum levofloxacin concentrations of about 4.0 and 6.7 µg/ml in the blister fluid were reached 2 - 4 hours after administration following 3 days dosing at 500 mg once or twice daily respectively. Blister Fluid/plasma rate is approximately 1.

Penetration into Bone Tissue
Levofloxacin is well penetrated to the cortical and spongiform tissues of the proximal and distal femur with the penetration rates within the range of 0.1 to 3. The maximum concentration of levofloxacin in the spongios proximal femur after 500 mg p.o. is about 15.1 mcg/g after 2 hours.

Penetration into Cerebro-Spinal Fluid
Levofloxacin has poor penetration into cerebro-spinal fluid.

Penetration into prostatic tissue
After administration of oral 500 mg levofloxacin three times a day, the mean concentration in prostatic tissue was 8.7 mcg/g after 2 hours on average and the mean prostate/plasma concentration was 1.84.

Concentration in urine
The mean urine concentrations 8-12 hours after a single oral dose of 150 mg, 300 mg or 500 mg levofloxacin were 44 mg/L, 91 mg/L and 200 mg/L, respectively

Biotransformation:
Levofloxacin is metabolised to a very small extent, the metabolites being desmethyl-levofloxacin and levofloxacin N-oxide. These metabolites are excreted in urine and account for < 5% of the dose. 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 total body clearance of levofloxacin following a 500 mg single dose was 175 ± 29.2 ml/min.
The mean total body clearance of levofloxacin following a 750 mg single dose was 143 ± 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/Non-Linearity:
Levofloxacin obeys linear pharmacokinetics over a range of 150 to 600 mg.

Special populations

Patients 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:

Cl_{cr} [ml/min]	< 20	20-49	50-80
Cl_R [ml/min]	13	26	57
$t_{1/2}$ [h]	35	27	9

Elderly:

There are no significant differences in levofloxacin pharmacokinetics between young and elderly subjects, except those associated with differences in creatinine clearance.

Gender differences:

Separate analysis for male and female subjects showed small to marginal gender differences in levofloxacin pharmacokinetics. There is no evidence that these gender differences are of clinical relevance.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential and toxicity to reproduction and development.

Levofloxacin caused no impairment of fertility or reproductive performance in rats and its only effect on fetuses was delayed maturation as a result of maternal toxicity.

Levofloxacin did not induce gene mutations in bacterial or mammalian cells but did induce chromosome aberrations in Chinese hamster lung cells in vitro. These effects can be attributed to inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unscheduled DNA synthesis, dominant lethal tests) did not show any genotoxic potential.
Studies in the mouse showed levofloxacin to have phototoxic activity only at very high doses. Levofloxacin did not show any genotoxic potential in a photomutagenicity assay, and it reduced tumour development in a photocarcinogenity study.

In common with other fluoroquinolones, levofloxacin showed effects on cartilage (blistering and cavities) in rats and dogs. These findings were more marked in young animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride,
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2 Incompatibilities
LEVOXIPOLIN is compatible with the following solutions for infusion:
0.9% sodium chloride solution
5% dextrose solution
2.5% dextrose solution
Ringer solution
Isolated balanced electrolyte solution
10% aminoacid solution

LEVOXIPOLIN must not be mixed with heparin or alkaline solutions (e.g. sodium bicarbonate).

6.3 Shelf life
24 months

6.4 Special precautions for storage
Store at room temperature below 25°C and in its packaging. Protect from light. Once removed from the package, the shelf life in the room is 3 days.

6.5 Nature and contents of container
100 mL transparent polypropylene bag, closed with SFC Port, in aluminum twinbag.

6.6 Special precautions for disposal and other handling
Do not throw away drugs that have expired or are not used! Give to the collection system determined by the Ministry of Environment and Urbanism.

7. MARKETING AUTHORISATION HOLDER
Name: POLİFARMA İLAÇ SANAYİ VE TİC. A.Ş.
Address: Vakıflar OSB Mahallesi,
Sanayi Caddesi, No:22/1
Ergene/TEKİRDAĞ
Tel : (0282) 675 14 04
Fax : (0282) 675 04 05

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