PATIENT INFORMATION LEAFLET

WARNING: SERIOUS SIDE EFFECTS INCLUDING TENDINITIS and TENDON RUPTURE (inflammation or tearing of tissues connecting muscles to bones), PERIPHERAL NEUROPATHY (disorders of the distant nerves for any reason - loss of sensation), central nervous system (central nervous system) EFFECTS and exacerbation of MYASTHENIA GRAVIS (a type of muscle weakness disease)

Antibiotics called fluoroquinolone, including levofloxacin, one of the active ingredients in MULTİFLEX LEVOFLEX, can cause injuries and irreversible undesirable effects such as:

- **Tissue that connects muscles to bones (tendinitis; symptoms may be severe pain in joints, swelling and redness) and tearing of tissue (tendon) connecting muscles to bones, (symptoms may be severe pain in muscles, sudden and rapid bruising, weakness, inability to move)**
- **Disorders seen in distant nerves for any reason- loss of sensation (peripheral neuropathy; symptoms may include pain in the nerves, tenderness, numbness in the feet and hands, numbness in the muscles, weakness in the hands, tremor in the hands).**
- **Central nervous system (central nervous system) effects (symptoms of vision (hallucination), anxiety (anxiety), mental breakdown (depression), suicidal tendencies, insomnia, severe headache and confusion of mind (confusion) can be)**

If you experience any of these undesirable effects during the use of MULTİFLEX LEVOFLEX, stop using MULTİFLEX LEVOFLEX immediately and talk to your doctor or pharmacist.

- **Antibiotics called fluoroquinolone, including levofloxacin, the active ingredient in MULTİFLEX LEVOFLEX, can exacerbate muscle weakness in patients with myasthenia gravis (a type of muscle weakness disease). If you have a known muscle weakness, talk to your doctor or pharmacist before using MULTİFLEX LEVOFLEX.**

MULTİFLEX LEVOFLEX 500 mg / 100 mL I.V. solution for infusion

Sterile

Administered by intravenously.

- ***Active Ingredient:*** Contains 512.48 mg levofloxacin hemihydrate, equivalent to 500 mg levofloxacin in 100 mL infusion solution
- ***Excipients:*** Sodium chloride, hydrochloric acid, sodium hydroxide (for pH adjustment), water for injection

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use high or low doses other than the recommended dosage.*

What is in this leaflet:

1. What MULTİFLEX LEVOFLEX is and what it is used for?

MULTİFLEX LEVOFLEX is a clear, greenish yellow solution applied intravenously. MULTIFLEX LEVOFLEX is in polypropylene (non-PVC) bags containing a total of 100 mL of solution, each containing 5 mg of levofloxacin in 1 ml.

MULTIFLEX LEVOFLEX is an antibiotic effective against bacteria. It is included in the group of antibiotics called fluoroquinolon. It prevents to growth, proliferation of bacteria and eliminates them. MULTIFLEX LEVOFLEX is used in the treatment of infections caused by bacteria that are susceptible to levofloxacin, the active substance of it.

Your doctor may prescribe this intravenous MULTIFLEX LEVOFLEX because you are unable take oral antibiotic treatment for one of the following conditions:

- Community-acquired pneumonia (pneumonia)
- Complicated renal and urinary tract infections including inflammation of the urinary tract and kidney(pyelonepphritis)

- Prostate inflammation
- Complicated skin and soft tissue infections: Uncomplicated skin and skin structure infections caused by wound infection including abscesses, cellulitis, furuncle, impetigo(deep infectious superficial microbial infection), pyoderma(purulent skin infection)
- Hospital-acquired pneumonia
- Exposure to airbone anthrax microbes

2. What you need to know before you use MULTİFLEX LEVOFLEX

DO NOT USE MULTİFLEX LEVOFLEX

If ;

- You are allergic to levofloxacin, any other floroquinolone antibiotics, or any of the other ingredients of this medicine,
- You have ever had epilepsy
- You have ever had a problem with your tendons such as tendonitis that was related to treatment with a 'quinolone antibiotic'. A tendon is the cord that joins your muscle to your skeleton.
- You are pregnant,
- You are breast-feeding ,
- You are a child or a growing teenager
- It should not be used in children, in growing adolescents, during pregnancy and in breastfeeding women because of the risk of damage to the developing cartilage tissue.

USE MULTİFLEX LEVOFLEX CAREFULLY if you;

Serious adverse reactions that cause injury and potentially irreversible, including tendinitis (swelling, pain around the joint) and tendon rupture, peripheral neuropathy (pain, numbness, needling and muscle weakness at the ends of the body) and central nervous system effects.

Fluoroquinolones, including MULTİFLEX LEVOFLEX, have been associated with serious side effects that can cause injury and are potentially irreversible. Common side effects include: muscle skeleton and peripheral nervous system (tendon inflammation, tendon rupture, swelling or inflammation of tendons, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, swelling in joints) atralji (joint pain), myalgia (muscle pain), peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendencies, insomnia, severe headache and confusion of mind).

These effects can be seen within hours or weeks of starting MULTİFLEX LEVOFLEX. Patients from all age groups or who did not have pre-existing risk factors experienced these side effects.

MULTİFLEX LEVOFLEX should be discontinued immediately if initial signs or symptoms of any serious side effects occur. Also, use of fluoroquinolones, including MULTİFLEX

LEVOFLEX, should be avoided in patients who experience any of these serious side effects in connection with fluoroquinolones.

If,

- You have a very severe lung infection or a serious hospital infection (use of another antibiotic may be more appropriate)
- You have a condition that concerns your central nervous system and you have experienced involuntary contractions related to it
- You have brain damage due to stroke or other brain injures
- You suffer from enteritis with bloody, watery diarrhea due to prolonged use of antibiotics: Severe, persistent and/or bloody diarrhea occurs during or after MULTİFLEX LEVOFLEX treatment, MULTİFLEX LEVOFLEX treatment should be terminated immediately and appropriate supportive and/or specific treatment should be initiated without delay. Contact your doctor immediately. Your doctor will prescribe the appropriate treatment for you.
- Risk of tendon rupture increase in elderly and in patients who use corticosteroids and when pain, redness, limitation of movement occurs in the tendons that may suggest inflammation or rupture. Your doctor may want to monitor this situation closely.
- You have renal failure: Your doctor will adjust the dose for you.
- It has been reported that patients who use MULTİFLEX LEVOFLEX rarely develop sensitivity to light. Do not expose to strong sunlight or artificial ultraviolet rays such as solarium during the use of MULTİFLEX LEVOFLEX and for 48 hours after the treatment.
- Superinfection (the beginning of a second infection in the structure weakened by ny infection): As with other antibiotics, long term use can result in excessive proliferation of non-resistant organisms. Your doctor may want to monitor you closely to prevent this condition. Superinfection occurs; appropriate treatment methods will be applied.
- You have prolonged QT interval(a condition that can lead to severe arrhythmias and sudden deaths in the hearth): Very rarely, prolongation of QT interval has been reported in patients using fluoroquinolone, including levofloxacin. Care is required in following risk groups:
    - If you have elderly(over 65 years) or female
    - If you have experienced a liver problem
    - If you have using corticosteroids
    - Uncorrected electrolyte imbalance (e.g. low levels of potassium and magnesium)
    - Congenital QT syndrome(a condition that can lead to serious cardiac arrhythmias and sudden deaths)
    - Hearth disease (hearth failure, history of heart attack, slowing of hearth beat)
    - Co-administration of drugs known prolong the QT interval(e.g. Class IA and III rhythm regulating drugs, some depression drugs, macrolide antibiotics and antipsychotics)

- You have an innate deficiency of an enzyme called glucose-6-phosphate
- Hypoglycemia (decrease in blood sugar level) and hyperglycemia(increase in blood sugar level): If you have diabetes and you are using insulin or oral medication, your blood sugar may decrease or an associated coma may occur or your blood sugar may rise (your doctor may ask you to check your blood sugar regularly).
- You have peripheral neuropathy (disorders that occur for any reason in the nerves-sensory loss).
- Exacerbation of Myasthenia Gravis (a kind of muscle weakness disease)
- Fluoroquinolones have an activity that inhibits muscle-nerve conduction and may exacerbate muscle weakness in patients with myasthenia gravis. Post-marketing serious side effects, including respiratory failure requiring respiratory support and death have been associated with fluoroquinolone in patients with myasthenia gravis using fluoroquinolone. Patients with a history of myasthenia gravis should avoid fluoroquinolone use.
- Hypersensitivity reactions: Following the first dose, severe hypersensitivity reactions (swelling of the face and throat due to allergy), which are seldom lethal, can be seen. You should stop your treatment and ask your doctor for urgent medical care.
- Severe diseases with blisters on the skin: MULTİFLEX LEVOFLEX can lead to severe skin reactions such as Stevens-Johnson syndrome (inflammation with infiltration swelling and redness on the skin and around the eyes), and toxic epidermal necrolysis (a serious disease with blisters on the skin). In this case, please contact your doctor immediately before continuing treatment.
- Very rarely, a single dose of levofloxacin can lead to suicidal thoughts and dangerous behavior. In this case, your doctor may stop your treatment and prescribe an appropriate treatment for you.
- If you have a history of psychological or psychiatric disorder, use MULTİFLEX LEVOFLEX with caution
- If you experience loss of appetite, jaundice, dark urine, itching or tenderness during your treatment, contact your doctor immediately. Your doctor may stop your treatment and prescribe an appropriate treatment for you.

If these warnings are valid for you, even in any period in the past, please consult your doctor.

Use of MULTİFLEX LEVOFLEX with food and drink

No interaction with food and drink because of the method of administration.

Pregnancy

Consult your doctor or pharmacist before using this medicine.

No adequate data is available on the use of levofloxacin in pregnant women. The potential risk to humans is unknown. MULTİFLEX LEVOFLEX should not be used during pregnancy due to insufficient data on humans and experimental studies with fluoroquinolones show a risk of damaging weight-bearing cartilage in growing organisms.

If you notice that you are pregnant during treatment, immediately consult your doctor or pharmacist.

Breast-feeding

Consult your doctor or pharmacist before using this medicine.

The are no or insufficient information on the excretion of levofloxacin into human or animal milk. The risk for the breastfed child cannot be ruled due to physicochemical and available pharmacodynamics/toxicological data for the excretion of levofloxacin by milk. MULTIFLEX LEVOFLEX should not be used during breastfeeding since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism.

Driving and using machines

Use of MULTİFLEX LEVOFLEX may cause some undesirable effects such as dizziness/vertigo, visual disturbances, drowsiness 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 car or operating machinery.
Patients who experience such side effects when using MULTİFLEX LEVOFLEX should not driving a car or operating machinery.

Important information about some of the excipients in MULTİFLEX LEVOFLEX

If you are not hypersensitive to the excipients contained in MULTİFLEX LEVOFLEX, an adverse effect is not expected.

This medicine contains 15,4 mmol (354 mg) of sodium per 100 mL dose. This should be taken into consideration by patients on a controlled sodium diet.

Other medicines and MULTİFLEX LEVOFLEX

- Theophylline, a drug that facilitates breathing by enlarging the bronchi (when combined with MULTIFLEX LEVOFLEX, the contraction threshold in the brain decreases)

- Non-steroidal anti-inflammatory drugs (NSAIDS) - such as fenbufen, ketoprofen, ibuprofen, aspirin and indomethacin. (You are more likely to have a fit (seizure) if taken with MULTİFLEX LEVOFLEX.)

- Probenecid – used for gout and cimetidine – used for ulcers and heartburn. (Reduces the excretion of MULTİFLEX LEVOFLEX from the body)

- Cyclosporine, a drug that suppresses the immune system (prolongs its half-life)

- Vitamin K antagonists used to prevent blood clotting(e.g. warfarin):The effect may increase, risk of bleeding may occur. Your doctor may request blood clotting tests.

- Drugs known to prolong the QT interval in heart (It may cause abnormal heart rhythm):
    - Class IA antiarrhythmic(quinidine) and Class III antiarrhythmic (amiodarone)
    - Some drugs for depression e.g. (tricyclic antidepressants such as amitriptyline and imipramine)
    - Macrolides (an antibiotic group)
    - Antipsychotics (used for psychiatric disorders)
- Corticosteroids (used for inflammation and asthma)

- Urine tests may show ‘false-positive’ results for strong painkillers called ‘opiates’ in people having this drug.

Other drugs: MULTİFLEX LEVOFLEX was not affected when was administered together with the following drugs: digoxin, glibenclamide and ranitidine.

Please inform your doctor or pharmacist if you are currently using any prescription or non-prescription medicine or if you have recently used it.

3. How to use MULTİFLEX LEVOFLEX

MULTİFLEX LEVOFLEX is administered by slow intravenous infusion (infusion lasting at least 60 minutes) by health staff.

MULTİFLEX LEVOFLEX is used in adults.

The dose will depend on the type and severity of infection and also on the sensitivity of the bacterium, which is the causative agent of the infection.

Depending on your condition, it may be possible to change from initial intravenous administration to oral administration (levofloxacin 500 mg tablets) at the same dosage within a few days.

MULTİFLEX LEVOFLEX is recommended the following doses:

Indication	**Daily dose** *(according to severity of infection)*	**Duration of treatment**
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Urinary tract and kidney inflammation (Pyelonephritis)	500 mg once daily	7 - 10 days
Complicated renal and urinary tract infections	500 mg once daily	7-14 gün
Skin and soft tissue infections	250 mg once daily or 500 mg one or twice daily	7 - 14 days
Prostate inflammation	500 mg once daily	28 days
Hospital-acquired pneumonia	750 mg once daily	10 - 14 days
Exposure to airbone anthrax microbes	500 mg once daily	8 weeks

The duration of treatment depends on the course of the disease (see table above). As with all antibiotic treatments in general, the use of MULTİFLEX LEVOFLEX should be continued for at least 48-72 hours after the patient’s fever go down and evidence of bacterial eradication has been

obtained.

Method of administration

MULTİFLEX LEVOFLEX is administered by slow intravenous infusion by health staff.
The infusion time must be 60 minutes or more for 500 mg MULTİFLEX LEVOFLEX solution.

The solution must be visually inspected before use. Only clear solutions without particles should be used.

100 mL Polypropylene bag, in aluminum over-pouch, closed with twist-off cover. After being removed from the outer packaging (aluminum overpouch), the shelf life is 3 days. Once the twist-off is punctured, it should be used immediately (within 3 hours). This medicinal product is for single use only.

Sunlight protection

Keep out of direct sunlight while having this medicine. Because your skin will become much more sensitive to the sun and may burn, tingle or severely blister. Therefore, use high factor sun cream. Wear a hat and clothes which cover your arms and legs. Avoid sun beds.

Different age groups

Use in children:

MULTİFLEX LEVOFLEX must not be given to children and growing adolescents.

Use in the elderly:

No adjustment of dose is required in the elderly, if there is no impairment of renal function.

Special cases for use:

Renal failure:

If you have impaired renal function, your doctor will reduce the dose of MULTİFLEX LEVOFLEX and monitor you more closely.

For patients with creatinine clearance less than 50 mL / min, the dosage will be determined by your doctor (depending on the severity of the infection)

Hepatic failure

No adjustment of MULTİFLEX LEVOFLEX dose is required in hepatic failure

Your doctor will tell you how long your treatment will take with MULTİFLEX LEVOFLEX. Do not stop your treatment without consulting your doctor.

If you have an impression that the effect of MULTİFLEX LEVOFLEX is too strong or weak, consult to your physician or pharmacist.

If you use more MULTİFLEX LEVOFLEX than you should have:

Consult to a physician or pharmacist if you have used more MULTİFLEX LEVOFLEX than you

should use.

MULTİFLEX LEVOFLEX will be administered by qualified medical personnel as often as your doctor considers it appropriate.

If you forget to use MULTİFLEX LEVOFLEX

Your doctor will decide when to administer the missed dose. Follow your doctor's instructions for the time of new administration of the following dose.

Do not use a double dose to make up for a forgotten dose.
Possible side effects one MULTİFLEX LEVOFLEX treatment is concluded

Do not stop your MULTİFLEX LEVOFLEX treatment without consulting your doctor, symptoms of your disease may reappear and resistance to bacteria may develop.

4. Possible side effects

Like all medicines, MULTİFLEX LEVOFLEX may have side effects in people who are sensitive to substances in its content.

Other side effects are classified as shown in the following categories:

Very common: Can be seen in at least one of 10 patients.
Common: Less than one in 10 patients, but more than one in 100 patients.
Uncommon: Less than one in 100 patients, but more than one in 1,000 patients.
Rare: Less than one in 1,000 patients, but more than one in 1,000 patients.
Very rare: less than one in 10,000 patients.
Unknown: cannot be estimated from the data available.

If you have any of the following, stop using MULTİFLEX LEVOFLEX and IMMEDIATELY tell your doctor or contact the emergency department of your nearest hospital:

Rare:
You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat, or tongue.

Unknown:
Stevens-Johnson syndrome, erythema multiforme (blood sitting on the skin and around the eye, inflammation with swelling and redness), toxic epidermal necrolysis (a serious disease in the skin with fluid-filled bubbles)

These are all very serious side effects. If you have one of these, you are severely allergic to MULTIFLEX LEVOFLEX. You may need urgent medical attention or hospitalization.

If you notice any of the following serious side effects, tell your doctor or contact the emergency department of your nearest hospital:

Rare:

- Pain and inflammation in your tendons or ligaments which could lead to rupture. The Achilles tendon is affected most often
- Fits (convulsions)

Unknown:

- Loss of appetite, yellowing of your skin or white of your eyes, dark colored urine, itching or abdominal pain or tenderness. These may be signs of liver problems that may be sometimes fatal.
- Exacerbation of myasthenia gravis(a type of muscle weakness disease)
- Alterations of the hearth rhythm, palpitations
- Fever, tingling, pain or lethargy. These may be symptoms of neuropathy.
- Severe cramp-like abdominal pain and high fever with severe, persistent, bloody diarrhea
- Rupture of joint ligaments and muscles, joint inflammation

These are all serious side effects. You may need urgent medical attention. Serious side effects are very rare.

Common:

- Nausea, vomiting, diarrhea
- Increase in the level of some liver enzymes in your blood
- Redness, pain, tenderness at the site of infusion
- Blood vessel inflammation (phlebitis)
- Headache, feeling dizzy
- Sleeping problems

Uncommon:

- Fungal infections, growth of resistance in other bacteria
- Itching and skin rash, severe itching or hives (urticaria), sweating too much (hyperhidrosis)
- Abdominal pain, indigestion, loss of appetite, feeling bloated (flatulence), constipation
- Dizziness (vertigo)
- Feeling stressed (anxiety), feeling confused, feeling nervous,
- Sleepiness, trembling, changes in the way things taste,
- Shortness of breath (dyspnea)
- Joint pain or muscle pain
- Blood tests may show unusual results due to liver (bilirubin increased) or kidney (creatinine increased) problems
- Decrease in the number of white blood cells (leukopenia)
- Fatigue

Rare:

- Reduced blood sugar. This is important for diabetic patients and may cause to coma.
- Psychiatric disorders that can accompany visual and auditory hallucinations

(hallucinations) and excessive skepticism (paranoia), restlessness, depression

- Abnormal dreams, nightmares
- Visual impairments including blurred vision
- Tinitus
- Muscle weakness. This is an important condition for patient with myasthenia gravis(a rare disorder of the nervous system)
- Low blood pressure
- Increased heartbeat, palpitations
- Decrease in the number of blood platelets (thrombocytopenia) leading to a deficiency to bruise and bleed easily
- Decrease in the number of white blood cells (neutropenia)
- Fever
- Alterations in kidney function and kidney failure which may be due to allergic kidney reactions called interstitial nephritis

Very rare:

- Attacks in patients with porphyria (a very rare metabolic disease)

Unknown:

- Coma associated with reduced blood sugar
- Increased blood sugar
- Self-destructive behavior, including suicidal thoughts and suicide attempts
- Loss of sense of taste
- Impaired sense of smell including loss of sense of smell
- Fainting (syncope), benign intracranial hypertension (benign pressure increase in the head)
- Impaired hearing ability, hearing loss
- Transient visual loss
- Increased skin sensitivity to sun and ultraviolet light (light sensitivity)
- Decrease in number of all blood cells (pancytopenia) or red blood cells (anemia).
- Pale and yellow skin due to the damage in red blood cells and the decrease in the number of all kinds of blood cells. Fever, sore throat and a general feeling of illness may occur
- Inflammation in the mouth (stomatitis)
- Excessive immune responses may develop (hypersensitivity).
- Movement and gait problems (dyskinesia, extrapyramidal disorder)
- Breathing difficulty and wheezing (bronchospasm)
- Allergy-induced pneumonia
- Inflammation of blood vessels caused by allergic reaction

- Inflammation of pancreas(pancreatitis)
- Pain (back, chest, arms and legs)

These are mild side effects of MULTİFLEX LEVOFLEX.

If symptoms such as this become uncomfortable or continue for a long time, contact your doctor.

If you notice any side effects not mentioned in this patient information leaflet, please inform your doctor or pharmacist.

5. How to store MULTİFLEX LEVOFLEX

Keep MULTİFLEX LEVOFLEX out of the reach and sight of children.
Keep at room temperature below 25 ° C and original package by protecting from light.

After being removed from the outer packaging (aluminum overpouch), the shelf life is 3 days.

Once the twist-off has been punctured (rubber stopper perforated) the solution should be used immediately (within 3 hours).

Use in accordance with the expiry date.

Do not use this medicine after the expiry date which is stated on the package.

Do not use *MULTİFLEX LEVOFLEX* if you notice that any defects in the product and / or packaging.

Marketing Authorization Holder **:** HAVER FARMA İlaç A.Ş.
Akbaba Mah. Maraş Cad.
No.:52/2/1 Beykoz / İstanbul

Manufacturing Site **:** Osel İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Caddesi No:52
Beykoz / İstanbul

This patient information leaflet approved in .../…/…

SUMMARY OF PRODUCT CHARACTERISTICS

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

- **Fluoroquinolones, including MULTİFLEX LEVOFLEX 500 mg/100 mL I.V. solution for infusion, can cause injury-causing and irreversible adverse reactions as follows:**

- Tendinitis and Tendon Rupture
- Periferal Neuropathy
- Central Nervous System Effects
In patients with any of these reactions, the use of MULTİFLEX LEVOFLEX should be discontinued immediately and fluoroquinolone use should be avoided.

- **Fluoroquinolones, including MULTİFLEX LEVOFLEX, may exacerbate muscle weakness in patients with myasthenia gravis. Avoid MULTİFLEX LEVOFLEX in patients with a known history of myasthenia gravis.**

1. NAME OF THE MEDICINAL PRODUCT

MULTİFLEX LEVOFLEX 500 mg/100 mL I.V. solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug substance:

100 ml solution for infusion,

Levofloxacin 500 mg (equivalent to 512.48 mg of Levofloxacin hemihydrate)

Excipient(s):

Sodium chloride 900 mg

Sodium hydroxide (for pH adjustment)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

In polypropylene (non-PVC) bags containing infusion solution

Clear, greenish-yellow solution

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MULTİFLEX LEVOFLEX is indicated for the treatment of the following infections in adults which caused bylevofloxacin-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 *Stapylococcus epidermidis*

- Skin and soft tissue infections:

Skin and skin strcture infections due to Methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes* or *Proteus mirabilis* and uncomplicated skin and akin structure infections including abscesses, cellulitis, furuncle, impetigo, pyoderma, wound infections, due to *Staphylococcus aureus or Streptococcus pyogenes*

- Hospital-acquired pneumonia:

Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Haemophilus influenzae or *Streptococcus pneumoniae.* when *Pseudomonas aeruginosa* is reported or suspected pathogen, an anti-pseudomonal ß-lactam combined treatment is recommended.

- Inhalation Anthrax:

Postexposure prophylaxis to airborne *Bacillus anthracis* and curative treatment.

Consideration should be given to official guidance on the appropriate use of antibacterial agents and local susceptibility of pathogens.(see section 4.4).

4.2. Posology and method of administration

MULTİFLEX LEVOFLEX is administered by slow intravenous infusion(infusion for at least 60 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 afterinitial IVadministration may be possible depending on patient's codition. Given the bioequivalence of the parenteral and oral forms, the same dosage can be used.

Posology:

The following dose recommendations for adults can be given for MULTİFLEX LEVOFLEX:

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

Indication	**Daily dosage** *(according to severity)*	**Total duration of treatment[1]** *(according to severity)*
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 gün
Prostatitis	500 mg once daily	28 days
Skin and soft tissue infections	250 mg once daily or one dose or 500 mg twice daily	7 - 14 days
Hospital-acquired pneumonia:	750 mg once daily	10 - 14 days
Inhalation anthrax	500 mg once daily	8 weeks

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

Method of Administration:

MULTİFLEX LEVOFLEX is only intended for slow intravenous infusion. It is administered once or twice daily. The infusion time must be at least 60 minutes for 500 mg MULTİFLEX LEVOFLEX (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 codition
For incompatibilities see section 6.2.

Duration of the treatment:

The duration of treatment depends on the course of the disease (see table above). As with all antibiotic treatments in general, the use of MULTİFLEX LEVOFLEX should be continued for at least 48-72 hours after the patient's fever go down and evidence of bacterial eradication has been obtained.

Additional information on special populations:

Renal failure:

Used as specified in the following table.

Dosage in patients that creatinine clearance ≤ 50 ml/min)(according to the severity of infection)

	250 mg/ 24 h	**500 mg/ 24 h**	**500 mg/ 12 h**
Creatinine clearance	**first dose 250 mg**	**first dose 500 mg**	**first dose 500 mg**
50 - 20 ml/min	*then:* 125 mg/24 h	*then:* 250 mg/24 h	*then:250* mg/12 h
19-10 ml/min	*then:* 125 mg/48 h	*then:* 125 mg/24 h	*then:* 125 mg/12 h
< 10 ml/min (including haemodialysis and 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:

MULTİFLEX LEVOFLEX 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

MULTİFLEX LEVOFLEX must not be used:

- In patients with known hypersensitivity to levofloxacin or to any other ingredients of MULTİFLEX LEVOFLEX or to any other antibacterial drug form 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 grpwing adolescents, during pregnancy, and in breast-feeding women based on animal studies, as the risk of damage to the developing cartilage tissue of developing organism cannot be completely ignored.

4.4. Special warnings and precautions for use

Disabling and potentially irreversible Serious adverse reactions including tendinitis, tendon rupture, peripheral neuropathy and central nervous system effects

Fluoroquinolones, including MULTİFLEX LEVOFLEX, 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, tendon swelling or inflammation, tingling or numbness, numbness of arms and legs, muscle pain, muscle weakness, joint pain, swelling of joints), atralgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendency, insomnia, severe headache and confusion). (see section 4.8).

These reactions can occur within hours or weeks after starting MULTİFLEX LEVOFLEX. Patients of all age groups or patients without pre-existing risk factors experienced these adverse reactions.

MULTİFLEX LEVOFLEX should be discontinued immediately if initial signs or symptoms of any serious adverse reactions occur. In addition, use of fluoroquinolones, including

MULTİFLEX LEVOFLEX, should be avoided in patients experiencing any of these serious adverse reactions in connection with fluoroquinolones.

General warnnigs
The prevalence of acquired resistance may vary from country to country and over time for some types of bacteria. For this reason, local data on resistance is needed; especially in severe infections or when no response to treatment is received, microbiological diagnosis should be made by isolating the pathogen and searching for evidence of the pathogen's susceptibility.
MULTİFLEX LEVOFLEX may not be the most appropriate treatment for very serious cases of pneumococcal pneumonia. Combined treatment may be needed in nosocomial infections caused by *P. aeruginosa*.

Methicillin-resistant *S. Aureus* (MRSA):
Methicillin-resistant *S. aureus* are very likely to possess co-resistance to fluoroquinolones, including levofloxacin. Therefore levofloxacin is not recommended for the treatment of known or suspected MRSA infections unless laboratory results have confirmed susceptibility of the organism to levofloxacin.

Convulsive patients:
MULTİFLEX LEVOFLEX, as with other quinolones, is contraindicated in patients with a history of epilepsy.

It should be used with great care in patients with a prior central nervous system lesion, who are prone to convulsion, who are taking fenbufen and similar non-steroid antiinflammatory drugs, or who are taking drugs that lower the cerebral convulsion threshold, such as theophyllin (see section 4.5). In case of convulsion type seizure, levofloxacin should be discontinued.

Clostridium difficile-associated disease (Pseudomembranous colitis):
Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with MULTİFLEX LEVOFLEX, may be symptomatic of pseudomembranous colitis of *Clostridium difficile*-associated disease. This is the most severe form of pseudomembranous colitis. If pseudomembranous colitis is suspected, MULTİFLEX LEVOFLEX should be stopped immediately and appropriate supportive and/or specific treatment(i.e. oral vancomycin, teicoplanin or metronidazole) initiated without delay. Anti-peristaltic medicinal products are contraindicated in this clinical situation.

Tendonitis and tendon rupture
Tendonitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. Tendonitis and tendon rupture, sometimes bilateral, may occur within 48 hours of starting treatment with levofloxacin. The risk of tendonitis and tendon rupture is increased in elderly patients, in patients receiving daily doses of 1000 mg and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if they are prescribed MULTİFLEX LEVOFLEX. All patients should consult their physician if they experience symptoms of tendonitis. If tendonitis is suspected, treatment with levofloxacin must be halted immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

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

Severe 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, primarily in patients with severe underlying diseases, e.g. sepsis (see section 4.8). Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

QT interval prolongation:
Very rarely, prolongation of the QT interval has been reported in patients receiving fluoroquinolone containing 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.

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 (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 MULTİFLEX LEVOFLEX should be adjusted in patients with renal impairment (see section 4.2).

Photosensitisation:
Photosensitization due to levofloxacin is very rarely seen. It is recommended that patients should not expose themselves unnecessarily to strong sunlight or to artificial UV rays (e.g. solarium), during treatment and for 48 hours following treatment discontinuation in order to prevent photosensitisation.

Superinfection:
The use of levofloxacin, especially if prolonged, 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 has to be used in these patients, potential occurrence of haemolysis should be 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 MULTİFLEX LEVOFLEX is at least 60 minutes. During this time, the patient 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.

Patients treated with Vitamin K antagonists:
Due to possible increase in coagulation tests (PT/INR) and/or bleeding in patients treated with MULTİFLEX LEVOFLEX 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

selfendangering 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.

Sodium content:
This medicinal product contains 15.4 mmol (354 mg) sodium per 100 ml dose. İthis should be considered for patients on a 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 antiinflammatory 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 affect 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 (24%) and probenecid (34%). This is because both drugs are capable of blocking the renal tubular secretion of levofloxacin. However, at the tested doses in the study, the statistically significant kinetic differences are unlikely to be of clinical relevance.

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 carefully monitored 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 II antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4 QT interval prolongation).

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

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 advice

Pregnancy category is C.

No adequate data is available on the use of levofloxacin in pregnant women.

Women with child-bearing potential / Contraception

No adequate data is available on the use in women with childbearing potential.

Pregnancy

Studies on animals are inadequate in terms of pregnancy and/or embryonal/fetal development and/or/effects on birth and / or postpartum development (see sections 4.3 and 5.3). Potential risk to humans is unknown. However in the absence of human data and due to the experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism, MULTİFLEX LEVOFLEX must not be used during pregnancy.

Lactation

There is insufficient/limited information on the excretion of levofloxacin in human or animal milk.The risk for breastfed child cannot be ruled due to physicochemicl and vailable pharmacodynamic/toxicological data fort he excretion of levofloxacin by milk. In the absence of human data and since experimental data suggest a risk of damage by fluoroquinolones to the weightbearing cartilage of the growing organism, MULTİFLEX LEVOFLEX must not be used during breastfeeding (see sections 4.3 and 5.3).

Reproduction/Fertility

No adequate data is available on the effect of MULTİFLEX LEVOFLEX on reproduction

ability in human.

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. Patients who experience such side effects when using MULTİFLEX LEVOFLEX, should not drive or 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.
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, Pathogen resistance

Blood and lymphatic system disorders
Uncommon: Leukopenia, Eosinophilia
Rare: Neutropenia, Thrombocytopenia
Not known: Pancytopenia, Agranulocytosis, Haemolytic anaemia

Immune system disorders
Rare: Angioedema, Hypersensitivity
Not known: Anaphylactic shock, Anaphylactoid shock
Anaphylactic and anaphylactoid 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 e.g. hallucination, paranoia), Depression, Agitation, Abnormal dreams, Nightmares
Not known: Psychotic disorders with selfendangering behaviour including suicidal ideation or suicide attempt

Nervous system disorders
Common: Headache, Dizziness
Uncommon: Somnolence, Tremor, Dysgeusia
Rare: Paraesthesia, Convulsion (see section 4.4)

Not known: Peripheral sensory neuropathy (see section 4.4), Dyskinesia, Extrapyramidal disorder, Ageusia, Parosmia including anosmia, 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 loss, Hearing impaired

Cardiac disorders
Rare: Tachycardia, Palpitation
Not known: Ventricular tachycardia, Ventricular arrhythmia and ,Torsade de pointes which may result in cardiac arrest, electrocardiogram QT prolonged (see sections 4.4 QT prolonged and section 4.9)

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 (see section 4.4), 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 (see section 4.4), Hepatitis

Skin and subcutaneous tissue disorders
Uncommon: Rash, Pruritus, Urticaria, Hyperhidrosis
Not known: Toxic epidermal necrolysis, Stevens-Johnson syndrome(see section 4.4), Erythema multiforme, Photosensitivity reaction(see section 4.4) , Leukocytoclastic vasculitis, Stomatitis
Mucocutaneous reactions may sometimes ocur even after the first dose.

Musculoskeletal and connective tissue disorders
Uncommon: Arthralgia, Myalgia
Rare: Tendon disorders including tendonitis (see section 4.4) (e.g. Achilles tendon), Muscular weakness which may be of special importance in patients with Myasthenia Gravis (see section 4.4)

Not known: Rhabdomyolysis, Tendon rupture (e.g. Achilles tendon) (see section 4.4), Ligament rupture, Muscle rupture, Arthritis

Renal and Urinary 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 (including pain in back, chest, and extremities).

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

4.9 Overdose and thearapy

Signs:

According to toxicity studies in animals the most important signs to be expected following acute overdose of MULTİFLEX LEVOFLEX are central nervous system symptoms such as confusion, dizziness, impairment of consciousness, and convulsive seizures.
Confusional state, convulsion, hallucination, and tremor have been observed in post marketing experience. Reactions related to the Gastrointestinal system are nausea and mucous eresions.

According to clinical pharmacology studies performed with supra-therapeutic doses, prolongation was observed in the 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.. Antacids may be used to protect the 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. PHARMACOLOGICALPROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic grup: 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.

Mechanisms 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.

As *In vitro,* levofloxacin has been shown to be effective against the following pathogens:

Aerobic Gram-positive: *Bacillus anthracis, Corynebacterium diphtheriae, Enterococcus faecalis*, Enterecoccus* spp*, Listeria monocytogenes,* Coagulase-negative staphylococci (methicillin-susceptible)**, Staphylococcus aureus (methicillin-susceptible)*, Staphylococcus epidermidis(methicillin-susceptible), Staphylococcus saprophyticus,* Streptococci, group C and G*, Streptococcus agalactiae, Streptococcus pneumoniae (penicillin-susceptible/moderately resistant/resistant)*, Streptococcus pyogenes(penicillin-resistant/susceptible)*

Aerobic Gram-negative: *Acinetobacter baumannii, Acinetobacter spp, Actinobaccillus actinomycetemcomitans, Citrobacter freundii*, Eikenella corrodens, Enterobacter aerogenes, Enterobacter cloacae*, Enterobacter spp, Escherichia coli*, Gardnerella vaginalis, Haemophilus ducreyi, Haemophilus influenzae* (ampisiline resistant/susceptible), Haemophilus parainfluenzae*, Helicobacter pylori, Klebsiella oxytoca, Klebsiella pneumoniae*, Klebsiella spp, Moraxella catarrhalis (beta-lactamase-positive / beta-lactamase-negative)*, Morganella morganii*, Neisseria gonorrhoeae (penicillase-producing / non-penicillase-producing), Neisseria meningitidis, Pasteurella canis, Pasteurella dagmatis, Pasteurella multocida, Pasteurella spp, Proteus mirabilis*, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Providencia spp, Pseudomonas aeruginosa**, Pseudomonas spp, Salmonella spp, Serratia marcescens*, Serratia spp.*

Anaerobic: *Bacteroides fragilis, Bifidobacterium* spp*, Clostridium perfringens, Fusobacterium* spp*, Peptostreptococcus, Propionibacterium* spp*, Veillonella* spp.

Other: *Bartonella* spp, *Chlamydia pneumoniae*, Chlamydia psittaci, Chlamydia trachomatis, Legionella pneumophila*, Legionella* spp*, Mycobacterium* spp*, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma hominis, Mycoplasma pneumoniae* Rickettsia* spp*, Ureaplasma urealyticum.*

Moderately susceptible microorganisms:

Aerobic Gram-positive: *Corynebacterium urealyticum, Corynebacterium xerosis, Enterococcus faecium, Staphylococcus epidermidis* (methicillin-susceptible), *Staphylococcus haemolyticus* (methicillin-susceptible).

Aerobic Gram-negative**:** *Campylobacter jejuni/coli.*

Anaerobic: *Clostridium difficile, Prevotella* spp *and Porphyromonas* spp.

Resistant microorganisms:

Aerobic Gram-positive: *Corynebacterium jeikeium, Staphylococcus* coagulase negative methi-R, *Staphylococcus aureus* (methicillin-susceptible).
Aerobic Gram-negative: *Alcaligenes xylosoxidans*

Anaerobic: *Bacteriodes thetaiotaomicron.*

Other: *Mycobacterium avium*

* Clinical efficacy has been proven in clinical trials.

** Nosocomial infections caused by *Pseudomonas aeruginosa* may require combination therapy.

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	>2mg/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

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 - 2 h. (Cmaks: 5.2±1.2 mcg/ml following the administration of single dose of 500 mg levofloxacin,) The absolute bioavailability is 99 - 100%. Levofloxacin shows linear pharmacokinetic properties in the 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 following table shows the peak and trough plasma concentrations of multiple oral or IV 500 mg dosing administered every day or every two days at tenth day:

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

* The infusion time for 500 mg IV 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 and 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 of bronchial mucosa, epithelial mucus fluid and alveaolar macrophages

After Single dose 500 mg p.o., the maximum levofloxacin concentrations in the bronchial mucosa and epithelial mucus fluid were 8.3 μg / ml and 10.9 μg / ml, respectively and serum penetration rate from the mucosa and epithelial mucosa are 1.1-1.8 and 0.8-3 respectively. These levels were reached approximately 1 hour or 4 hours after administration, respectively.
Following 500 mg and 750 mg oral administration for 5 days, the mean concentrations in epithelial mucus fluid 4 hours after the last administration were 9.94 mcg / ml and 22.12 mcg / ml, respectively. The alveolar macrophage was 97.9 mcg / ml and 105.1 mcg / ml, respectively.

Penetration of lung tissue

After 500 mg p.o., the maximum levofloxacin concentrations in the lung tissue were 11.3 μg/g, and these levels were reached about 4-6 hours after administration and the distribution rate from lung tissue to plasma was 2-5.

Penetration of bullous fluid

2-4 hours after administration of the 500 mg dose once or twice daily for 3 days, maximum levofloxacin concentrations of 4.0 and 6.7μg/ml were achieved in bullous fluid, with a bullous fluid / plasma ratio of approximately 1.

Distribution to bone tissue

Levofloxacin penetrates well into the proximal and distal femoral cortical and spongy tissue penetration rates from 0.1 to 3. Following 500 mg p.o., the maximum concentration of levofloxacin in the spongios proximal femur is approximately 15.1 mcg/g 2 hours after administration.

Penetration of cerebro-spinal fluid

Levofloxacin has poor penetration to cerebro-spinal fluid.

Distribution to prostate tissue

After administration of oral 500 mg levofloxacin 3 times daily, the mean concentration in prostate tissue was 8.7 μg / g after an average of 2 hours and the average prostate / plasma concentration was 1.84.

Concentration in urine

After an oral single dose of 150 mg, 300 mg or 500 mg, the average urine concentrations of 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 account for <5% of the dose and are excreted in urine. Levofloxacin is stereochemically stable and does not undergo chiral inversion.

Elimination:

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½ :6-8 h). Excretion is primarily by the renal route (>85% of the administered dose).

The mean apparent total body clearance of levofloxacin following a 500 mg single dose was 175 +/-29.2 ml/min.
The mean apparent total body clearance of levofloxacin following a 750 mg single dose was 143 +/-29.1 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
$t_{1/2}$ [hour]	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

Hydrochloric acid

Sodium hydroxide (for pH adjustment)

Water for injection

6.2 Incompatibilities

MULTİFLEX LEVOFLEX must not be mixed with heparin or alkaline solutions (e.g. sodium hydrogen carbonate).

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at room temperature below 25 ° C and original package by protecting from light.

After being removed from the outer packaging (aluminum overpouch), the shelf life in the room light is 3 days.

6.5 Nature and contents of container

Polyolefin bag in aluminium over-pouch, closed with twist-off cover, single port, medium and inner layer polyolefin-based polypropylene, outer layer only made of polypropylene, 100ml.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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