Module 1.3.1.1 Summary of Product Characteristics

Summary of Product Characteristics of Multiflex Levoflex 500 mg/100 mL I.V. Solution for Infusion was presented on following pages.

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 bags containing greenish-yellow-clear I.V. Solution for Infusion

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.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

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.

<u>Biotransformation:</u>

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

In 100 ml PP bag with single output with protective Al overpouch.

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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