SUMMARY OF PRODUCT CHARACTERISTICS

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

- Fluoroquinolones, including BERAXİN, can cause irreversible adverse effects that can lead to disabilities, as follows
  - Tendinitis and tendon rupture
  - Peripheral neuropathy
  - Effects on central nervous system

  In patients with any of these reactions, BERAXIN should be discontinued immediately and fluoroquinolones should be avoided.

- Fluoroquinolones, including BERAXIN, may exacerbate muscle weakness in patients with myasthenia gravis. The use of BERAXIN should be avoided in patients with a known history of myasthenia gravis.

- Since it is known that fluoroquinolone group drugs, including BERAXIN, is associated with serious adverse reactions, it can be used in the following indications if there are no other alternatives.
  - Acute bacterial sinusitis
  - Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT
BERAXIN 500 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each film coated tablet contains;

Active substance(s):
Levofloxacin 500 mg (equivalent to 512.46 mg levofloxacin hemihydrate)

Excipients:
Ponso 4R lacquer (E124)……..0.0052 mg
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film coated tablet
Yellow film-coated oblong tablet with a score on one side

4. CLINICAL PARTICULARS
4.1. Therapeutic indications
It should not be used in acute bacterial sinusitis and acute bacterial exacerbation of chronic bronchitis in the presence of alternative treatment options due to the risk of serious side effects.

BERAXIN is indicated for the treatment of the following infections in adults, which are caused by microorganisms sensitive to levofloxacin:
• Acute sinusitis

caused by *Streptococcus pneumoniae, Haemophilus influenzae, or Moraxella catarrhalis*

• Acute exacerbation of chronic bronchitis
Caused by *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae or Moraxella catarrhalis*

• Community acquired pneumonia
Caused by *Staphylococcus aureus, Streptococcus pneumoniae* (including penicillin-resistant strains with an MIC ≥ 2 microgram/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
Complicated infections of the skin and skin appendages caused by methicillin-susceptible *Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes or Proteus mirabilis* and uncomplicated infections of the skin and skin appendages, including abscess, cellulitis, furuncle, impetigo, pyoderma, wound infections caused by *Staphylococcus aureus or Streptococcus pyogenes*

• Anthrax Inhalation
Prophylaxis and curative treatment after exposure to airborne *Bacillus anthracis*

Official national guidelines on the appropriate use of antibacterial agents and local susceptibility of pathogens should be considered (See Section 4.4).

4.2. Posology and method of administration
Posology/frequency of administration and duration of the treatment:

BERAXIN is administered once or twice daily. The dosage depends on the type and severity of the infection as well as the susceptibility of the causative pathogen.

BERAXIN is recommended to be administered for adults at the following doses:

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

Indication	**Daily dose regimen** *(according to severity)*	**Duration of treatment** (*according to severity)*
Acute sinusitis**	500 mg once daily	10 – 14 days
Acute exacerbation of chronic bronchitis**	250 – 500 mg once daily	7 – 10 days
Community-acquired pneumonia	500 mg once or twice daily	7 – 14 days
Pyelonephritis	500 mg once daily *	7 – 10 days
Complicated urinary tract infections	500 mg once daily	7 – 14 days
Skin and soft tissue infections	250 mg once daily or 500 mg	7 – 14 days

	once or twice daily	
Chronic bacterial prostatitis	500 mg once daily	28 days
Anthrax inhalation	500 mg once daily	8 weeks

**Dose escalation should be considered in severe infections.*
***For oral use only*

Method of administration:
BERAXIN should be swallowed without crushing and with a sufficient amount of liquid. It can be divided at the score line to adapt the dosage. The film-coated tablets may be taken during meals or between meals. BERAXIN should be taken at least two hours before or after administration of antacids containing iron salts, zinc salts, magnesium or aluminum, or didanosine (only dianosine formulations with buffering agents containing magnesium or aluminum) and sucralfate, since reduction of absorption can occur. (See Section 4.5)

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

Additional information for special populations:
Renal failure:
It is used as indicated in the table below.

Dosage in patients with creatinine clearance ≤ 50 ml/min (depending on 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 hemodialysis 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 in hepatic failure since levofloxacin is not metabolized to any relevant extent by the liver and is mainly excreted by the kidneys.

Pediatric population:
BERAXIN is contraindicated in children and growing adolescents. (See Section 4.3)

Geriatric population:
In elderly patients, no dose adjustment is required if renal function is adequate. (See Section 4.4, QT interval prolongation)

4.3. Contraindications
BERAXIN (levofloxacin) must not be used:
- in patients with known hypersensitivity to levofloxacin or any of the excipients in BERAXIN or to another antibacterial drug of 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

Use in children, growing adolescents, during pregnancy and lactating women is contraindicated because, based on animal studies, the risk of damage to the developing cartilage tissue of the growing organism cannot be completely excluded.

4.4. Special warnings and precautions for use

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

Fluoroquinolones, including BERAXIN, have been associated with serious adverse reactions that can cause disability and are potentially irreversible. Common adverse reactions are musculoskeletal and peripheral nervous system disorders (such as tendonitis, tendon rupture, swelling or inflammation of tendons, tingling or numbness, numbness in arms and legs, myalgia, muscle weakness, arthralgia, swelling in joints), atralgia, myalgia, peripheral neuropathy and central nervous system diseases (hallucination, anxiety, depression, suicidality, insomnia, severe headache and confusion) (See Section 4.8).

These reactions may occur within hours or weeks of starting BERAXIN. Patients of all age groups or without pre-existing risk factors have experienced these adverse reactions.

BERAXIN should be discontinued immediately at the first signs or symptoms of any serious adverse reaction. In addition, the use of fluoroquinolones, including BERAXIN, should be avoided in patients experiencing any of these serious adverse reactions in association with fluoroquinolones.

General warnings

The prevalence of acquired resistance may vary from country to country and over time for some bacterial strains. Therefore, local data on resistance is needed. Especially in severe infections or when there is no response to treatment, microbiological diagnosis should be made by isolating the pathogen and evidence of the sensitivity of the pathogen should be sought.

BERAXIN 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*:

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.

Patients predisposed to seizures

As with other quinolones, BERAXIN is contraindicated in patients with a history of epilepsy. It should be used with extreme caution in patients with pre-existing central nervous system lesions, prone to convulsions, taking fenbufen and similar non-steroidal anti-inflammatory

drugs, or taking drugs that lower the cerebral convulsion threshold, such as theophylline (see section 4.5). In case of convulsive seizure, treatment with levofloxacin should be discontinued.

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

Tendonitis and tendon rupture
Tendinitis may rarely occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. This undesirable effect may occur within 48 hours of starting treatment and may be bilateral. The risk of tendon rupture is increased in the elderly, in patients taking corticosteroids, and taking doses of 1000 mg daily. Close monitoring of these patients is therefore necessary if they are prescribed BERAXIN. All patients should consult their physician if they experience symptoms of tendinitis. If tendonitis is suspected, treatment with BERAXIN should be discontinued immediately and appropriate treatment should be initiated, such as immobilization of the affected tendon.

Hypersensitivity reactions

Levofloxacin can rarely cause serious, potentially fatal hypersensitivity reactions (e.g. angioedema, anaphylactic shock) following the initial dose (see section 4.8). Patients should stop treatment immediately and consult a doctor for immediate action.

Severe bullous reactions
Severe bullous skin reactions such as Stevens Johnson syndrome or toxic epidermal necrolysis have been reported with levofloxacin (see section 4.8). If any skin and/or mucous membrane disorders occur, patients should consult their physician immediately before continuing treatment.

Hepato-biliary disorders
Cases of hepatic necrosis up to fatal hepatic failure have been reported with levofloxacin in patients with very severe underlying diseases such as 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 loss of appetite, jaundice, dark urine, pruritus or tender abdomen.

QT interval prolongation
QT prolongation has been reported very rarely in patients receiving fluoroquinolones, including levofloxacin.

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

- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- 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, cisapride)

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.

Dysglycemia
As with all quinolones, disturbances in blood glucose, including hyperglycaemia and hypoglycaemia, have been reported in patients with diabetes, usually treated with an oral hypoglycemic agent (e.g. glibenclamide) or insulin. Cases of hypoglycemic 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. Post-marketing serious adverse reactions, including lung failure requiring respiratory support and death, have been associated with fluoroquinolone use in patients with myasthenia gravis. The use of fluoroquinolones should be avoided in patients with a history of myasthenia gravis.

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

Development of sensitivity to light (photosensitization)
Although photosensitization with levofloxacin is very rare, it is recommended that patients should not expose to sunlight or to artificial ultraviolet rays such as a solarium during the treatment and for 48 hours following treatment discontinuation.

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

Patients with glucose-6-phosphate dehydrogenase deficiency
Patients with latent or actual defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone antibacterial agents. Therefore levofloxacin should be used with caution in such patients.

Peripheral neuropathy
Sensory or sensory-motor peripheral neuropathy, which may be rapid in its onset, has been reported in patients receiving fluoroquinolones, including levofloxacin. To prevent the development of irreversible disorders, levofloxacin should be discontinued if the patient experiences symptoms of neuropathy.

Anthrax inhalation
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.

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

Psychotic reactions
Psychotic reactions have been reported in patients receiving quinolones, including levofloxacin. In very rare cases these have progressed to suicidal thoughts and self-endangering behaviour- sometimes after only a single dose of levofloxacin (see section 4.8). In the event that the patient develops these reactions, levofloxacin should be discontinued and appropriate measures should be taken. 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 tests
In patients treated with levofloxacin, determination of opiates in urine may give false-positive results. It may be necessary to confirm positive opiate screens by more specific method.

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

The excipient ponso 4R lac (E124), used as a colorant in BERAXIN, may cause allergic reactions in sensitive individuals.

4.5. Interaction with other medicinal products and other forms of interaction

Medicines containing magnesium and aluminum or iron and zinc, didanosine
Since the absorption of levofloxacin is significantly reduced when administered with preparations such as iron salts containing divalent or trivalent cations, or with drugs containing magnesium and aluminum (e.g. antacids), these medicines should be administered at least two hours before or 2 hours after administration of BERAXIN (see section 4.2).

Calcium salts have a minimal effect on the oral absorption of levofloxacin.

Sucralfate
The bioavailability of BERAXIN is significantly reduced when administered together with sucralfate. If the patient is to receive both sucralfate and BERAXIN, it is best to administer sucralfate 2 hours after the BERAXIN administration (see section 4.2).

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 drugs that lower the seizure threshold, theophylline or nonsteroidal anti-inflammatory drugs are used together with a quinolone group antibiotic.

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 co-administered with drugs that reduce tubular renal secretion, such as probenecid and cimetidine, especially in patients with renal impairment.

Probenecid and cimetidine had a statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin was decreased by 24% with cimetidine and by 34% with probenecid. 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 III antiarrhythmics, tricyclic antidepressants, macrolides and, antipsychotics cisapride) (see section 4.4. QT interval prolongation)

Other
Clinical pharmacology studies have shown that there is no clinically significant change in the pharmacokinetics of levofloxacin when administered with digoxin, glibenclamide, ranitidine, and calcium carbonate.

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

Food
There is no clinically relevant interaction with food. BERAXIN may therefore be administered regardless of food intake.

Additional information for special populations:
No interaction studies have been conducted in special populations.

Pediatric population:
No interaction studies have been conducted in the pediatric population.

4.6. Fertility, pregnancy and lactation
General advice
Pregnancy category: C.
There are no adequate data from the use of levofloxacin in pregnant women.

Women of childbearing potential/Birth control (contraception)
Insufficient data are available on use in women of childbearing potential.

Pregnancy
Animal studies are insufficient with respect to pregnancy / and-or / embryonal / fetal growth / and-or /natal / and-or / postnatal development. (See section 4.3 and 5.3). Potential risk is not known for human. BERAXIN should not be used during pregnancy because of insufficient

human data and experimental studies with fluoroquinolones have shown the risk of damaging weight-bearing cartilage in growing organisms.

Breastfeeding
There is insufficient/limited information regarding the excretion of levofloxacin in human or animal milk. Due to the physicochemical and pharmacodynamic/toxicological data regarding excretion of levofloxacin in milk, a risk for the breastfed child cannot be excluded. BERAXIN should not be used during breast-feeding because of the risk of damage to weight-bearing cartilage in growing organisms in experimental studies with fluoroquinolones. (See Sections 4.3 and 5.3).

Reproductive ability / fertility
There are no adequate data on the reproductive ability of BERAXIN in humans.

4.7. Effects on ability to drive and use machines
The use of BERAXIN may cause some undesirable side effects such as drowsiness/dizziness, visual disturbances, somnolence, which may impair the patient's ability to concentrate and react. In situations that require special attention, such as driving and using machinery, a reduction in these abilities may pose a risk. Patients who experience such side effects while using BERAXIN should not drive or use machines.

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' (frequency can not be estimated from the available data).

Undesirable effects presented within each frequency group are ranked in order of decreasing severity.

Infections and infestations
Uncommon: Fungal infections, pathogen resistance

Blood and lymphatic system disorders
Uncommon: Leukopenia, eosinophilia
Rare: Neutropenia, thrombocytopenia
Not known (post-marketing data): Pancytopenia, agranulocytosis, haemolytic anaemia

Immune system disorders
Rare: Angioedema, hypersensitivity
Not known (post-marketing data): Anaphylactic shock, anaphylactoid shock.
Anaphylactic and anaphylaxis-like reactions can 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, hypoglycemic coma (see section 4.4)

Psychiatric disorders
Common: insomnia
Uncommon: Anxiety, confusional state, nervousness
Rare: Psychotic disorder (e.g. with hallucinations and paranoia), depression, agitation, abnormal dreams, nightmares
Not known (post-marketing data): Psychotic reactions with self-endangering behavior including suicidal ideation and suicide attempt

Nervous system disorders
Common: Headache, dizziness
Uncommon: Somnolence, tremor, dysgeusia
Rare: paresthesia, convulsions (see section 4.4)
Not known (post-marketing data): Sensory and sensory-motor peripheral neuropathy (see section 4.4), dyskinesia, extrapyramidal disorder, olfactory disorders (parosmia), including loss of taste (agusia), loss of sense of smell (anosmia), syncope, benign intracranial hypertension

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

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

Cardiac disorders
Rare: tachycardia, palpitation
Not known (post-marketing data): Torsade de pointes, which may result in cardiac arrest, ventricular arrhythmia, ventricular tachycardia, electrocardiogram QT prolonged (see section 4.4, QT interval prolongation and section 4.9)

Vascular disorders
Rare: hypotension

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea
Not known (post-marketing data): bronchospasm, pneumonitis allergic

Gastrointestinal disorders
Common: Diarrhoea, vomiting, nausea
Uncommon: Abdominal pain, dyspepsia, flatulence, constipation
Not known (post-marketing data): Hemorrhagic diarrhea, which in very rare cases may be indicative of enterocolitis, including pseudomembranous colitis (see section 4.4), pancreatitis

Hepato-biliary disorders
Common: Hepatic enzyme increased (ALT/AST, alkaline phosphatase, GGT)
Uncommon: Blood bilirubin increased
Not known (post-marketing data): Severe liver injury, jaundice

Cases of acute hepatic failure, sometimes fatal, have been reported with levofloxacin, primarily in patients with severe underlying disease (see section 4.4), hepatitis.

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, rash, 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
Sometimes mucocutaneous reactions may occur even after the first dose.

Musculoskeletal, connective tissue and bone disorders
Uncommon: Arthralgia, myalgia
Rare: Tendon disorders including tendinitis (e.g. Achilles tendon) (see section 4.4), muscular weakness which may be of special importance in patients with myasthenia gravis (see section 4.4 exacerbation of myasthenia gravis)
Not known (post-marketing data): Rhabdomyolysis, tendon rupture (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
Uncommon: Asthenia
Rare: fever
Not known: Pain (including pain in back, chest, and extremities)

Other undesirable effects associated with administration of fluoroquinolones
Very rare: attacks of porphyria in patients with porphyria

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Turkish Pharmacovigilance Center (TÜFAM). (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; tel.: 800 314 00 08; fax: 0 312 218 35 99)

4.9 Overdose and treatment
Symptoms:

According to toxicity studies in animals, the most important signs to be expected following acute overdosage of BERAXIN are confusion, drowsiness, impairment of consciousness and convulsive seizures. Central nervous system effects, including confusional state, convulsions, hallucinations and tremor, have been observed in post-marketing experience. Reactions related to the gastrointestinal tract are nausea and mucosal erosions.

Prolongation of the QT interval has been observed in clinical pharmacology studies with supra therapeutic doses.

Treatment:

In the event of overdose, the patient should be carefully monitored, ECG monitoring should be undertaken as there is a possibility of prolongation of the QT interval and symptomatic treatment should be implemented. Antacids may be used for protection of gastric mucosa.

Hemodialysis, peritoneal dialysis, or continuous ambulatory peritoneal dialysis are not effective in removing levofloxacin from the body. There is no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.l. Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials, fluoroquinolones

ATC Code: J01MA12

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class and is the S (-) enantiomer of the racemic drug substance ofloxacin.

Mechanism of action

As a fluoroquinolone antibacterial agent, levofloxacin acts on DNA gyrase complex and topoisomerase IV.

Antibacterial spectrum

Rates of resistance may vary geographically and over time for the strain selected, and local information for resistance patterns should be considered, especially in the treatment of severe infections.

In vitro, levofloxacin has been shown to be active 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*, C and G group streptococci, *Streptococcus agalactiae, Streptococcus pneumoniae* (penicillin-susceptible/moderately resistant/resistant)*, *Streptococcus pyogenes**, Viridans streptococci (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** (ampicillin susceptible/resistant), *Haemophilus parainfluenzae*, Helicobacter pylori, Klebsiella oxytoca, Klebsiella pneumoniae*, Klebsiella* spp, *Moraxella catarrhalis* (beta-lactamase-positive /beta-lactamase-negative)*, *Morganella morganii*, Neisseria gonorrhoeae* (penicylase-producing/non-penicylase-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.*

Intermediate susceptible microorganisms:
Aerobic Gram-positive: *Corynebacterium urealyticum, Corynebacterium xerosis, Enterococcus faecium, Staphylococcus epidermidis* (methicillin resistant), *Staphylococcus haemolyticus* (methicillin resistant) **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 resistant) **Aerobic Gram-negative:** *Alcaligenes xylosoxidans* **Anaerobic:** *Bacteriodes thetaiotaomicron* **Other:** *Mycobacterium avium*
* Clinical efficacy has been proven in clinical studies.
*** Combination therapy may be required in nosocomial infections caused by Pseudomonas aeruginosa.*

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 European Committee for Antimicrobial Susceptibility Testing (EUCAST recommended MIC breakpoints for levofloxacin, separating susceptible from intermediately susceptible organisms and intermediately susceptible from resistant organisms are presented in the below table for MIC testing (mg/l).
EUCAST clinical MIC breakpoints for levofloxacin (version 2.0, 2012-01-01):

Pathogen	**Susceptible**	**Resistant**
Enterobacteriacae	≤1 mg/l	>2 mg/l
Pseudomonas spp.	≤1 mg/l	>2 mg/l
Acinetobacter spp.	≤1 mg/l	>2 mg/l
Staphylococcus spp.	≤1 mg/l	>2 mg/l
S. pneumoniae [1]	≤2 mg/l	>2 mg/l
Streptococcus A,B,C,G	≤1 mg/l	>2 mg/l
H. influenzae [2,3]	≤1 mg/l	>1 mg/l
M. catarrhalis [3]	≤1 mg/l	>1 mg/l

Non-species related[4]	≤1 mg/l	>2 mg/l
1. Levofloxacin breakpoints are associated with high-dose therapy. 2. Low-level fluoroquinolone resistance (ciprofloxacin MIC 0.12-0.5 mg/l) may occur, but there is no evidence of clinical significance of this resistance in respiratory tract infections caused by H influenzae. 3. Strains with MICs above the susceptible breakpoints are very rare or not reported. Identification or antimicrobial susceptibility testing on any of these isolates should be repeated, and if the result is confirmed, the isolate should be sent to the reference laboratory. Confirmed isolates with an MIC above the current resistance breakpoint should be reported as resistant until evidence of clinical response is available. 4. Breakpoints apply to oral doses of 500 mg x 1 - 500 mg x 2 and intravenous doses of 500 mg x 1 - 500 mg x 2.		

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

5.2 Pharmacokinetic properties

General characteristics

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed with peak plasma concentrations being obtained within 1 h. The absolute bioavailability is 100%. Food has little effect on the absorption of levofloxacin.

Distribution:

Approximately 30-40% of levofloxacin is bound to serum protein.

A negligible accumulation was observed with multiple doses of levofloxacin 500 mg daily. There is a small amount of accumulation after administration of 500 mg twice daily.

Penetration into tissues and body fluids*:*

Penetration into bronchial mucosa, epithelial lining fluid, alveolar macrophages

After a single dose of 500 mg PO, the maximum levofloxacin concentrations in the bronchial mucosa and epithelial lining fluid are 8.3 microgram/ml and 10.9 microgram/ml, respectively, and the penetration rates from the mucosa and epithelial lining fluid to the serum are 1.1-1.8 and 0,8-3 respectively. These levels were reached approximately 1 hour or 4 hours after administration, respectively.

Following oral administration of 500 mg and 750 mg for 5 days, mean concentrations in epithelial lining fluid 4 hours after the last administration were 9.94 micrograms/ml and 22.12 micrograms/ml, respectively. It is 97.9 microgram/ml and 105.1 microgram/ml in alveolar macrophage, respectively.

Penetration into Lung Tissue

The maximum concentrations of levofloxacin in lung tissue after a 500 mg PO dose are 11.3 micrograms/g, and these levels are reached approximately 4-6 hours after administration, with a distribution ratio of 2-5 from lung tissue to plasma.

Penetration into the Bladder Fluid

Maximum levofloxacin concentrations of 4 and 6.7 micrograms/ml, respectively, in the bladder fluid were reached 2-4 hours after administration of the 500 mg dose once or twice daily for 3 days, with a bladder fluid/plasma ratio of approximately 1.

Distribution in Bone Tissue
Levofloxacin penetrates well into cortical and spongy tissue in the proximal and distal femur, with penetration rates of 0.1 to 3. The maximum concentration of levofloxacin in the spongios proximal femur after 500 mg PO is approximately 15.1 micrograms/g 2 hours after administration.

Penetration into Cerebro-Spinal Fluid
The penetration of levofloxacin into the cerebro-spinal fluid is low.

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

Concentration in Urine
Mean urinary concentrations of levofloxacin after a single oral dose of 150 mg, 300 mg, or 500 mg are 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 isomeric inversion.

Elimination:

Following oral and intravenous administration of levofloxacin, it is eliminated relatively slowly from the plasma (t½: 6 - 8 hours). 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 total body clearance of levofloxacin following a single 750 mg dose is 143 ± 29.1 ml/min.

There is no fundamental pharmacokinetic difference between intravenous and oral administration of levofloxacin, suggesting that the oral and intravenous routes may be interchangeable.

Linarity/Non-linearity:
In the 150-600 mg dose range, levofloxacin follows a linear pharmacokinetics.

Patient characteristics
Patients with renal failure:
The pharmacokinetics of levofloxacin are affected by renal failure. With decreasing renal function, renal elimination and clearance decreased and elimination half-life 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 subjects:
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
Preclinical 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.

As 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.l. List of excipients
Tablet core
Microcrystalline cellulose PH 102
Hydroxypropyl methyl cellulose
Crospovidone
Sodium stearyl fumarate

Film coating agent (Opadry II Yellow)
Talc
Polyvinyl alcohol
Polyethylene glycol
Ponso 4R Lacquer (E 124)
Titanium dioxide (E 171)
Quinoline yellow aluminum lacquer (E 104)

6.2. Incompatibilities
Not reported.

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 25°C. Keep out of reach of children and in its package.

6.5. Nature and contents of container
BERAXIN is marketed as 7 tablets in PVC/PE/PVDC aluminum blisters.

6.6. Special precautions for disposal and other handling
Unused product or waste materials should be disposed of in accordance with the 'Medical Waste Control Regulation' and 'Packaging Waste Control Regulation'.

7. MARKETING AUTHORISATION HOLDER
Berko İlaç ve Kimya San. A.Ş.
Yenişehir Mah. Özgür Sok. No: 16-18 Ataşehir/İstanbul-Turkey
+90 216 456 65 70 (Pbx)
+90 216 456 65 79 (Fax)
info@berko.com.tr

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