

SUMMARY PRODUCT CHARACTERISTICS

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

Fluoroquinolones, including RAVIVO have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together including:

- Tendinitis and tendon rupture
- Peripheral neuropathy
- Central nervous system effects

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

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

Since fluoroquinolone group drugs, including RAVIVO, are known to be associated with serious adverse reactions, the following indications may be used if there are no other alternatives.

- Acute bacterial sinusitis
- Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT

RAVIVO 500 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

Levofloksasin 500 mg (equivalent to 512,46 mg levofloksasin hemihydrate)

Excipients:

Please refer to 6.1 for other excipients.

3. PHARMACEUTICAL FORM

Film coated tablet

White, oblong, notched, film coated tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute bacterial sinusitis should not be used due to the risk of serious side effects in the presence of alternative treatment options for acute bacterial exacerbation of chronic bronchitis. In addition, the sensitivity of urinary infections should be proven by antibiogram.

RAVIVO is indicated for the treatment of the following adult infections caused by levofloxacin-sensitive microorganisms:

- 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*

- Pneumonia, obtained in society

Caused by *Staphylococcus aureus*, *Streptococcus pneumoniae* (including penicillin resistant strains of which MIC value for penicillin ≥ 2 $\mu\text{g/ml}$), *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Chlamydia pneumoniae*, *Legionella pneumophila* or *Mycoplasma pneumoniae*

- Urinary system infections with complications, including pyelonephritis

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

- Prostatitis:

Caused by *Escherichia coli*, *Enterococcus faecalis* or *Stapylococcus epidermidis*

- Skin and soft tissue infections

Methicillin-sensitive *Staphylococcus aureus*, *Enterococcus faecalis*, *Streptococcus pyogenes*, or *Proteus mirabilis* caused complicated skin and skin infections and abscess, cellulitis, furuncles, impetigo, pyoderma, complicated skin and skin add infections, including wound infection, caused by *Staphylococcus aureus* or *Streptococcus pyogenes*

- Anthrax Inhalation

Prophylaxis and curative treatment after exposure to airborne *Bacillus anthracis*

Official national guidelines should be considered for appropriate usage of antibacterial agents

and local sensitivity of pathogens (see Section 4.4).

4.2 Posology and method of administration

RAVIVO is applied once or twice a day. The dosage depends on the type and severity of the infection and also on the sensitivity of the pathogen.

Posology:

RAVIVO is recommended for adults in the following doses:

Dosage for patients with normal kidney functions (creatinine clearance > 50ml/min)

Indication	Daily dosage (according to severity of the infection)	Usage Period (according to severity of the infection)
Acute sinusitis**	Daily single dose 500 mg	10-14 days
Acute exacerbation of chronic bronchitis**	Daily single dose 250-500 mg	7-10 days
Community acquired pneumonia	Daily single dose or 2 times 500 mg	7-14 days
Pyelonephritis	Daily single dose 500 mg*	7-10 days
Complicated urinary system infections	Daily single dose 500 mg*	7-14 days
Chronic bacterial prostatitis	Daily single dose 500 mg	28 days
Skin and soft tissue infections	Daily single dose 250 mg or Single dose or twice 500 mg	7-14 days
Anthrax inhalation	Daily single dose 500 mg	8 weeks

* Dosage increase should be considered for severe infection cases.

**Just for oral use.

Method of administration:

RAVIVO should be swallowed with sufficient amount of liquid without being crushed. It can be divided by the notch line to comply with the dosage. Film-coated tablets can be taken with or between meals. As the absorption may be reduced RAVIVO iron salts, zinc salts, magnesium or aluminum-containing antiacids or didanosine (didanosine formulations with only buffers containing magnesium or aluminum) should be taken at least two hours before or after the application of sucralfate. (See Section 4.5)

Treatment period

Treatment period depends on course of the disease (refer to the table above). In general, like in all antibiotic treatments, RAVIVO administration should be continued for at least

another 48-72 hours after lowering the fever of the patients and supply of evidences for obtaining bacterial eradication.

Additional information of the special population:

Kidney failure:

Used according to the table mentioned below.

Dosage for patients with kreatinine clearance ≤ 50 ml/minute (according to the severity of the infection)

	250 mg / 24 hours	500 mg / 24 hours	500 mg / 12 hours
Kreatinine clearance	Initial dose 250 mg	Initial dose 500 mg	Initial dose 500 mg
50-20 ml/min	<i>then:</i> 125 mg/24 hours	<i>then:</i> 250 mg/24 hours	<i>then:</i> 250 mg/12 hours
19-10 ml/min.	<i>then:</i> 125 mg/48 hours	<i>then:</i> 125 mg/24 hours	<i>then:</i> 125 mg/12 hours
< 10ml / min	<i>then:</i> 125 mg/48 hours	<i>then:</i> 125 mg/24 hours	<i>then:</i> 125 mg/24 hours

(along with hemodialysis and continual ambulatory peritoneal

** There is no need for an additional dosage after hemodialysis or during continual ambulatory peritoneal dialysis.*

Liver failure:

RAVIVO metabolizes in liver with very small amounts and in principle it is removed from body by means of kidneys. Therefore, there is no need for dosage adjustment during liver failure.

Pediatric population:

RAVIVO is contraindicated for children and growth continuing teenagers (See Section 4.3).

Geriatric population:

If kidney functions are at sufficient levels there is no need for dosage adjustment to old.
(ref. Section 4.4, Extension of QT interval)

4.3 Contraindications

In the following mentioned situations, RAVIVO (levofloxacin) should not be used:

- Patients, known to be very sensitive against levofloxacin or any agent within the compound of RAVIVO infusion solution or any other antibacterial drug of fluorocinolone group
- Patients with epilepsy
- Patients with tendon disorder background, known to develop in connection with usage of an antibacterial drug of fluorocinolone group
- Children and still growing teenagers
- During pregnancy
- Women who are breastfeeding
- In children, the growth of adolescents who continue to grow, during pregnancy and in women who are breastfeeding is contraindicated because the risk of damaging the developing organism's developing cartilage tissue cannot be completely ignored - based on animal studies.

4.4 Special warnings and precautions for use

Serious adverse reactions that lead to disability and potentially irreversible, including the effects of tendonitis and tendon rupture, peripheral neuropathy, and central nervous system:

Fluoroquinolones, including RAVIVO, have been associated with potentially irreversible serious adverse reactions that can lead to disability. Common adverse reactions are musculoskeletal and peripheral nervous system (such as tendonitis, tendon rupture, tendon swelling or inflammation, tingling or numbness, numbness in arms and legs, muscle aches, muscle weakness, joint pain, swelling in the joints), arthralgia, 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 be seen within hours or weeks after the start of RAVIVO. Patients of all age groups or those who do not have pre-existing risk factors, experience these adverse

reactions.

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

General warnings

The prevalence of acquired resistance may vary over time and from country to country for some bacterial species. Therefore, local data on resistance are needed; especially in severe infections or when no response to treatment can be achieved, the pathogen must be isolated and microbiological diagnosis should be established and evidence of the susceptibility of the pathogen should be sought.

For very severe cases of pneumococcal pneumonia RAVIVO it may not be the most appropriate treatment.

Combined therapy may be needed in nosocomial infections caused by *P. aeruginosa*.

Methicillin-resistant *S. aureus* :

Methicillin-resistant *S. aureus* is likely to resistance fluoroquinolones, including levofloxacin. Therefore, the use of levofloxacin in the treatment of known or suspected MRSA infections is not recommended unless the organism's susceptibility to levofloxacin is confirmed by laboratory tests.

Patients susceptible to convulsions:

As with other quinolones, RAVIVO is contraindicated in patients with a history of epilepsy.

It should be used with caution in patients with a previous central nervous system lesion, prone to convulsion, receiving fenbufen and similar non-steroidal antiinflammatory drugs, or taking cerebral convulsion thresholds such as theophylline. (See Section 4.5). Levofloxacin treatment should be discontinued if convulsion type seizure occurs.

Disease associated with Clostridium difficile (Pseudomembranous colitis)

If severe, persistent and / or bloody diarrhea occurs during or after RAVIVO treatment, this may be a sign of pseudomembranous colitis associated with *Clostridium difficile*. This is the most severe form of pseudomembranous colitis. If pseudomembranous enterocolitis is suspected, RAVIVO treatment should be discontinued immediately and appropriate supportive

and / or specific treatment (eg oral vancomycin, teicoplanin or metranidazole) should be initiated without delay. In this clinical situation, drugs that inhibit bowel movements are contraindicated.

Tendinitis and tendon rupture:

Tendinitis may occur rarely. It affects the Achilles tendon most and may lead to tendon rupture. This undesirable effect may occur within 48 hours after starting treatment and may be bilateral. The risk of tendon rupture was increased in elderly patients and patient who are taking corticosteroids. If RAVIVO be prescribed to these patients, they must be closely monitored. All patients who experience symptoms of tendinitis must inform their doctor. If tendonitis is suspected, RAVIVO treatment should be discontinued immediately and the affected tendon should be immobilization and appropriate therapy initiated.

Hypersensitivity reactions:

Levofloxacin rarely may cause severe hypersensitivity reactions (eg, angioedema, anaphylactic shock) with a lethal potential following its initial dose (See Section 4.8). Patients should discontinue treatment and contact the doctor immediately for urgent action.

Heavy bullous reactions:

Stevens-Johnson syndrome or toxic epidermal necrolysis have been reported as severe bullous skin reactions with levofloxacin (see. Section 4.8). In case of any skin and / or mucosal disorder occur, patients should consult their physician immediately before continuing treatment.

Hepato-biliary disorders:

Patients with severe underlying diseases, such as sepsis, have been reported life-threatening liver failure, including liver necrosis with levofloxacin administration (See Section 4.8). If symptoms and signs of liver disease such as loss of appetite, jaundice, dark urine, itching or tenderness occur, the patient must stop treatment and contact the doctor immediately.

Prolongation of the QT interval:

In very rare cases QT interval prolongation has been reported in patients receiving fluoroquinolones, including levofloxacin.

In patients using fluoroquinolone, including levofloxacin, caution should be exercised if there are risk factors for prolongation of the QT interval as follows:

- Uncorrected electrolyte imbalance (eg. Hypokalemia, hypomagnesemia)
- Congenital long QT syndrome
- Cardiac disease (eg. Heart failure, myocardial infarction, bradycardia)
- Use of medications together known to prolong the QT interval (eg. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

Older patients and women may be more susceptible to drugs that prolong the QTc interval. Therefore, for fluoroquinolones, including levofloxacin, caution should be exercised when used in this patient group.

Dysglycemia:

As with all other quinolones, blood glucose level disorders, including hyperglycemia and hypoglycemia, have been reported in patients with diabetes generally treated with oral hypoglycemic agent (eg, glibenclamide) or insulin. Hypoglycemic coma have been reported. Careful monitoring of blood glucose is recommended in patients with diabetes. (See Section 4.8)

The exacerbation of myasthenia gravis:

Fluoroquinolones, including levofloxacin have neuromuscular blocking activity and they can exacerbate muscle weakness in patients with myasthenia gravis. In patients with myasthenia gravis using fluoroquinolone, severe post-marketing adverse events, including lung failure requiring ventilatory support, death, have been associated with fluoroquinolone. Patients with a history of myasthenia gravis should be avoided with fluoroquinolone.

Patients with renal failure :

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

Development of sensitivity to light (photosensitivity)

Although photosensitization due to levofloxacin is very rare, it is recommended that patients should not be exposed to strong sunlight for 48 hours after treatment is terminated or to be exposed to artificial ultraviolet rays such as solarium to prevent photosensitization.

The superinfection:

As with other antibiotics, prolonged use of levofloxacin may cause excessive growth of non-

resistant organisms. Repeated assessments of the patient's condition are critical. If superinfection occurs, appropriate treatment methods should be applied.

Glucose-6-phosphate dehydrogenase deficiency patients:

Patients with latent or current defects in glucose-6-phosphate dehydrogenase activity may be prone to hemolytic reactions when treated with quinolone group antibacterials, so levofloxacin should be used with caution in such patients.

Peripheral neuropathy:

Sensory or sensory-motor peripheral neuropathy, which may be rapid onset, has been reported in patients using fluoroquinolone, including levofloxacin. In order to prevent the development of irreversible disorders, the use of levofloxacin should be discontinued if the patient experiences symptoms of neuropathy.

Inhalation anthrax:

Human use is based on in vitro *Bacillus anthracis* susceptibility data, experimental data in animals, and limited data in humans. The treating physician should consult the national and / or international consensus documents on anthrax treatment.

Patients treated with vitamin K antagonists:

In patients treated with vitamin K antagonist (eg warfarin), coagulation tests should be followed in the case of co-administration of RAVIVO in case of coagulation tests (PT / INR) increase and / or increased bleeding (see section 4.5).

Psychotic reactions:

Psychotic reactions have been reported in patients receiving quinolone, including levofloxacin. In very rare cases, suicidal thoughts and self-endangering behaviors are sometimes seen following a single dose of levofloxacin (see section 4.8). If patients develop such reactions, levofloxacin should be discontinued and appropriate measures taken. Caution should be exercised if levofloxacin is required in patients with a psychotic disorder or a history of psychiatric disease.

Vision disorders

If any effects in the eyes or visual impairment occur, should be examined by the ophthalmologist immediately

(see Sections 4.7 and 4.8).

Interaction with laboratory tests

In patients treated with levofloxacin, false positive results may be obtained during the detection of opiates in urine. This result may need to be verified using more specific methods.

Levofloxacin may suppress the proliferation of *Mycobacterium tuberculosis* and therefore may have a false negative result in the bacteriological diagnosis of tuberculosis.

4.5 Interaction with other medicinal products and other forms of interaction

Magnesium or aluminum or drugs containing iron or zinc, didanosine

When combined with preparations such as iron salts containing divalent or trivalent cations or with drugs containing magnesium and aluminum (eg antacids), these drugs should be administered at least two hours before or after 2 hours of administration of RAVIVO, since the absorption of levofloxacin is markedly reduced (see section). 4.2).

Calcium salts have minimal effect on oral absorption of levofloxacin.

Sucralfate

The bioavailability of RAVIVO decreases significantly when administered with sucralfate. If the two drugs are to be administered together, it is recommended that sucralfate be administered at least two hours after administration of RAVIVO (see section 4.2).

Theophiline, fenbufen or similar other nonsteroidal anti-inflammatory drugs

In a clinical study, no pharmacokinetic interaction between levofloxacin and theophylline was found. However, drugs that reduce the convulsion threshold, theophylline or nonsteroidal anti-inflammatory drugs in combination with a quinolone group antibiotic, a significant decrease in the threshold of brain convulsion may be seen.

Compared to its sole application, the concentration of levofloxacin is approximately 13% higher when used in combination with fenbufen.

Probenecid and cimetidine

When levofloxacin administered with drugs that reduce its renal tubular secretion like probenecid and cimetidine, should be cautious particularly in patients with renal impairment.

Probenecid and cimetidine make statistically significant effect on the elimination of levofloxacin. The renal clearance of levofloxacin is reduced by 24% with cimetidine and 34%

with probenecid. This is because both drugs block the renal tubular secretion of levofloxacin. However, in the study, the kinetics differences which are statistically significant, it is unlikely clinically significant.

Cyclosporine

Half-life of cyclosporin is increased by 33% when administered with levofloxacin.

Vitamin K antagonists

Coagulation tests should be closely monitored in patients treated with vitamin K antagonists, coagulation tests (PT / INR) and / or severe increases in bleeding have been reported in patients treated with a vitamin K antagonist (eg warfarin) in combination with levofloxacin.

Patients should be followed carefully for signs of bleeding (See Section 4.4).

Drugs known to prolong the QT interval

Levofloxacin should be used with caution in patients receiving drugs known to prolong the QT interval (eg, Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) as in other fluoroquinolones (see section 4.4, Prolongation of QT interval).

Other

Clinical pharmacology studies, it has been shown that there is no clinical change in the pharmacokinetics of levofloxacin in combination with digoxin, glibenclamide, ranitidine and calcium carbonate.

Foods

Since there is no clinically significant interaction with foods, RAVIVO can be used independently of food intake.

Additional information about special populations

No interaction studies have been conducted with respect to specific populations.

Pediatric population:

No interaction studies have been conducted with regard to pediatric populations.

4.6 Pregnancy and lactation

General advice

Pregnancy category is C.

There is insufficient data on the use of levofloxacin in pregnant women.

Women with potential for giving birth to a child / Birth control (Contraception)

There is not enough data on the use of women with childbearing potential.

Pregnancy period

Animal studies are insufficient in terms of the effects on pregnancy and / or embryonal / fetal development and / or birth and / or postnatal development. (see Sections 4.3 and 5.3). The potential risk for humans is unknown. RAVIVO should not be used during pregnancy because the data related to humans are not sufficient and experimental studies with fluoroquinolones show the risk of damaging the weight bearing cartilage in growing organisms.

Lactation period

There is inadequate / limited information about levofloxacin being excreted with human or animal milk. Due to the physicochemical and pharmacodynamic / toxicological data available for the elimination of levofloxacin with milk, it may be considered a risk for the breast child. In experimental studies with fluoroquinolones, RAVIVO should not be used during breastfeeding because of the risk of damaging the weight bearing cartilage in growing organisms. (see Sections 4.3 and 5.3).

Reproduction ability / Fertility

There is not enough data on RAVIVO's ability to reproduce on humans.

4.7 Effects on ability to drive and use machines

The use of RAVIVO may cause some undesirable side effects such as dizziness, visual disturbances, drowsiness, which may impair the patient's concentration and responsiveness. Reduction in these capabilities may pose a risk in situations where special attention is required, such as vehicle and machine use. Patients who experience such side effects when using RAVIVO should not use vehicles and machinery.

4.8 Undesirable effects

The following information is based on data from clinical trials and post-marketing experiences involving more than 8300 patients.

Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1.000$ to $< 1/100$); rare ($\geq 1/10.000$ to $< 1/1.000$); very rare ($< 1/10.000$), unknown (cannot be estimated in

connection with obtained data).

The undesirable effects presented in each frequency group are listed according to the decreasing severity.

Infections and infestations

Uncommon: fungus infections, pathogen resistance

Blood and lymph system diseases

Uncommon: Leukopenia, eosinophilia

Rare: neutropenia, thrombocytopenia

Unknown (post-marketing data): Pancytopenia, agranulocytosis, hemolytic anemia

Immune system diseases

Rare: Angioedema , hypersensitivity

Unknown (post-marketing data): anaphylactic shock, anaphylactoid shock.

Sometimes even after the first dose of anaphylactic and anaphylactoid reactions may occur (see. Section 4.4).

Metabolism and nutrition disorders

Uncommon: Anorexia

Rare: hypoglycemia, especially in diabetic patients (See. Section 4.4)

Unknown: Hyperglycemia, Hypoglycemic coma (see. Section 4.4)

Psychiatric disorders

Common: insomnia

Uncommon: anxiety, confusional state, irritability

Rare: psychotic disorder (e.g. with hallucinations and paranoia), depression, agitation, abnormal dreams, nightmares

Unknown (post marketing information): Psychotic reactions with self-injurious behavior including suicidal thoughts and attempted suicide

Nervous system diseases

Common: Headache, dizziness

Uncommon: somnolence, tremor, altered taste disorders (dysgeusia)

Rare: paresthesia, convulsions (see. Section 4.4)

Unknown (post-marketing data): sensory and sensory-motor peripheral neuropathy (see. Section 4.4), dyskinesia, extrapyramidal disorder, sense of taste loss (aguz), odor disorders ((parosmia) including loss of sense of smell (anosmia), syncope, benign intracranial hypertension

Eye diseases

Rare: impaired vision including blurred vision

Unknown: Temporary visual loss (See section 4.4)

Ear and inner ear diseases

Uncommon: Vertigo

Rare: Tinnitus

Unknown: deterioration in hearing ability, loss on hearing

Cardiac disorders

Rare: Tachycardia, palpitations

Unknown (post-marketing data): Torsades de pointes which can result in cardiac arrest, ventricular arrhythmia, ventricular tachycardia, prolongation of QT interval on electrocardiogram (see section 4.4, prolongation of QT interval and Section 4.9).

Vascular disease

Rare: Hypotension

Respiratory, thoracic and mediastinal disorders diseases

Uncommon: dyspnea

Unknown (post-marketing data): bronchospasm, allergic pneumonia

Gastrointestinal disorders

Common: Diarrhoea, vomiting, nausea

Uncommon: Abdominal pain, dyspepsia, flatulence, constipation

Unknown (post-marketing data): hemorrhagic diarrhea - in very rare cases pseudomembranous colitis (see. Section 4.4), including enterocolitis can sign, pancreatitis

Hepato-biliary disorders

Common: increase in liver enzymes (ALT / AST, alkaline phosphatase, GGT)

Uncommon: Bilirubin increase in blood

Unknown (post-marketing data): Severe liver damage, jaundice

There have been reported cases of acute hepatic insufficiency that sometimes fatal, with levofloxacin in patients with primary underlying disease (see section 4.4), hepatitis. (see section 4.4).

Skin and subcutaneous tissue disorders

Uncommon: itching, redness, urticaria, hyperhidrosis

Unknown: Toxic epidermal necrolysis, Stevens-Johnson syndrome (see. Section 4.4), erythema multiforme, photosensitivity reactions (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. (See Section 4.4) (e.g. the Achilles tendon), particular importance in patients with myasthenia gravis is muscle weakness. (See Section 4.4 exacerbation of myasthenia gravis)

Unknown (post-marketing data): rhabdomyolysis, tendon rupture (eg. Achilles tendon) (see. Section 4.4) ligament rupture, muscle rupture, arthritis

Renal and urinary disorders

Uncommon: increased blood creatinine levels

Rare: Acute renal failure (eg. Connected to interstitial nephritis)

General disorders and administration site disorders

Uncommon: asthenia

Rare: Fever

Unknown: Pain (back, chest and extremities)

Other undesirable effects associated with administration of fluoroquinolones:

Very rare: attacks of porphyria in patients with porphyria disease

4.9 Overdose and treatment

Symptoms:

According to the toxicity studies in animals, the most important signs that should be expected in the case of acute overdose of RAVIVO are confusion, dizziness, impaired consciousness and convulsive seizures. The effects of the central nervous system, including confusion, convulsions, hallucinations and tremor, have been observed in post-marketing experience. Gastrointestinal system reactions are nausea and mucosal erosions.

Clinical pharmacology studies with supra therapeutic doses showed prolongation of QT interval.

Treatment:

In case of overdose, the patient should be monitored carefully, ECG follow-up should be performed and symptomatic treatment should be applied because of the possibility of prolongation of QT interval. Antacids can be applied to protect the gastric mucosa.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: quinolone antibacterials, fluoroquinolones

ATC code: J01MA12

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

Mechanism of Action

Levofloxacin as a fluoroquinolone antibacterial drug acts on DNA gyrase complex and topoisomerase IV.

Antibacterial spectrum

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

Levofloxacin has been shown to be effective in the following pathogens by in vitro:

Gram-positive aerobe: *Bacillus anthracis*, *Corynebacterium diphtheriae*, *Enterococcus faecalis**, *Enterococcus spp*, *Listeria monocytogenes*, *Koagülaz negatif stafilokoklar (metisiline duyarlı)*, *Staphylococcus aureus (metisiline duyarlı)**, *Staphylococcus epidermidis (metisiline duyarlı)*, *Staphylococcus saprophyticus*, *C ve G grubu streptokoklar*, *Streptococcus agalactiae*, *Streptococcus*

pneumoniae (penisiline duyarlı/orta düzeyde dirençli/dirençli)*, *Streptococcus pyogenes**, *Viridans streptokoklar* (penisiline dirençli/duyarlı) **Gram-negative aerobe:** *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 duyarlı/dirençli), *Haemophilus parainfluenzae**, *Helicobacter pylori*, *Klebsiella oxytoca*, *Klebsiella pneumoniae**, *Klebsiella spp*, *Moraxella catarrhalis* (beta-laktamaz-pozitif /beta- laktamaz-negatif)*, *Morganella morganii**, *Neisseria gonorrhoeae* (penisilaz üreten/ penisilaz üretmeyen), *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*. **Anaerobe:** *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 sensitive microorganisms:

Gram-positive aerobe: *Corynebacterium urealyticum*, *Corynebacterium xerosis*, *Enterococcus faecium*, *Staphylococcus epidermidis* (resistant to methicillin), *Staphylococcus haemolyticus* (resistant to methicillin).

Gram-negative aerobe: *Campylobacter jejuni/coli*

Anaerobe: *Clostridium difficile*, *Prevotella spp* and *Porphyromonas spp*

Resistant microorganisms:

Gram-positive aerobe: *Corynebacterium jeikeium*, *Staphylococcus coagulase negative methi-R*, *Staphylococcus aureus* (resistant to methicillin).

Gram-negative aerobe: *Alcaligenes xylosoxidans*,

Anaerobe: *Bacteriodes thetaiotaomicron*.

Other: *Mycobacterium avium*

* Clinical effects are proven with clinical studies.

** Combination treatment might be required for *pseudomonas aeruginosa* active neurochemical infections.

Resistance

Resistance to levofloxacin is achieved by a stepwise process with type II topoisomerase, DNA gyrase and topoisomerase IV target site mutations. Other resistance mechanisms, such as the permeation barrier (common in *Pseudomonas aeruginosa*) and pump mechanisms, may also affect the sensitivity to levofloxacin.

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

Limit Value

The recommended MIC limit values for levofloxacin are given in the following table by the European Committee for Antimicrobial Susceptibility Tests (EUCAST) in order to separate highly sensitive and sensitive and moderately sensitive and resistant organisms (MIC test-mg/l).

EUCAST clinical MIC limit values for levofloxacin (version2.0,2012-01-01):

Pathogen	Sensitive	Resistant
Enterobacteriaceae	≤1 mg/l	> 2 mg/l
<i>Pseudomonas spp.</i>	≤1 mg/l	> 2 mg/l
<i>Acinetobacter spp.</i>	≤1 mg/l	> 2 mg/l
<i>Staphylococcus spp.</i>	≤1 mg/l	> 2 mg/l
<i>S. pneumoniae</i>	≤2 mg/l	> 2 mg/l
<i>Streptococcus A,B,C,G</i>	≤1 mg/l	> 2 mg/l
<i>H. influenzae</i> ^{2,3}	≤1 mg/l	> 1 mg/l
<i>M. catarrhalis</i> ³	≤1 mg/l	> 1 mg/l
Limit values that is not intrinsic to species ⁴	≤1 mg/l	> 2mg/l
1. Limit values of levofloxacin 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 the clinical significance of this resistance in respiratory influenza infections caused by H. influenzae.

3. Strains with MIC values on sensitive cut-off values are very rare or not reported. The recognition or antimicrobial sensitivity tests performed in any of these isolates should be repeated and sent to the isolate reference laboratory if the result is confirmed. It should be reported as resistant until the evidence of clinical response to confirmed isolates that have a MIC value above the current resistance limit value appears.
4. The limit values are valid for oral 500mg x 1 - 500 mg x 2 and intravenous doses of 500 mg x 1 - 500 mg x 2.

Resistance prevalence may vary geographically and depending on the time of selected species. In particular, local resistance information is required for the treatment of severe infections. If necessary, in the situations that the use of the drug is questioned at least in some infections, expert advice should be sought for the prevalence of local resistance

5.2 Pharmacokinetic properties

General properties

Absorption:

Orally administered levofloxacin is rapidly and almost completely absorbed by obtaining peak plasma concentrations within 1 hour. Absolute bioavailability is 100%. Food has a small effect on the absorption of levofloxacin.

Distribution:

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

A negligible accumulation was observed with 500 mg multi-dose levofloxacin per day. After administration of 500 mg twice daily, there is a small amount of accumulation.

Transfer to tissues and body fluids:

Penetration to Bronchial Mucosa, Epithelial Mucus Fluid and Alveolar Macrophages

After 500 mg single oral administration, the maximum concentrations in bronchial mucosa and epithelial mucus fluid were 8.3 µg / g and 10.9 µg / ml, respectively. The rates of penetration into the serum from the mucosa and epithelial mucus fluid 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, the average concentrations in the epithelial mucus fluid after 4 hours of last administration were 9.94 mcg / ml and 22.12 mcg / ml, respectively. The alveolar macrophages were 97.9 mcg / ml and 105.1 mcg / ml, respectively.

Penetration into Lung Tissue

The maximum concentration of levofloxacin in lung tissue after an oral dose of 500 mg was 11.3 µg / g and these levels were reached approximately 4-6 hours after delivery and the distribution rate from lung tissue to plasma was 2-5.

Penetration into Bulla Fluid

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

Distribution of Bone Tissue

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

Cerebro-Spinal Fluid Penetration

Levofloxacin transition to cerebrospinal fluid is low.

Prostate tissue distribution

After oral administration of 500 mg levofloxacin in 3 times a day, the concentration following 2 hours on average in the prostate tissue was 8.7 µmikrog / g and the mean prostate / plasma concentration was 1.84.

Concentration in Urine

After 150 mg, 300 mg or 500 mg single oral dose of levofloxacin, average urine concentrations were 44 mg / L, 91 mg / L and 200 mg / L, respectively.

Biotransformation:

Levofloxacin is minimally metabolized, its metabolites desmethyl-levofloxacin and levofloxacin N-oxide. Metabolites are excreted in urine and constitute <5% of the dose. Levofloxacin is stereochemically stable and does not undergo isomeric transformation.

Elimination:

Levofloxacin is eliminated from plasma relatively slowly following oral and intravenous administration ($t_{1/2}$: 6 to 8 hours). Its excretion is mainly from the renal tract (> 85% of the administered dose).

The mean total body clearance of levofloxacin after a single dose of 500 mg was 175 ± 29.2 ml / min.

The mean total body clearance of levofloxacin after a single dose of 750 mg was 143 ± 29.1 ml / min.

There is no fundamental pharmacokinetic difference in intravenous and oral administration of levofloxacin, this suggests that oral and intravenous routes can be interchangeable.

Linearity / non-linearity status:

150-600 mg dose range, levofloxacin follows linear pharmacokinetics.

Characteristic of patients

Patients with kidney failure:

The pharmacokinetic properties of levofloxacin are affected in renal failure. With decreased kidney function, elimination and clearance from kidneys decreases and the elimination half-life is prolonged, as shown in the table below:

Cl _{cr} [ml/min]	< 20	20 - 49	50 - 80
Cl _R [ml/min]	13	26	57
$t_{1/2}$ [hr]	35	27	9

Elder patients:

The pharmacokinetic properties of levofloxacin, except those associated with differences in creatinine clearance, does not vary significantly between elderly and young people.

Gender differences:

As a result of separate analyzes in men and women, there were very small marginal differences between the sexes in the pharmacokinetic properties of levofloxacin. There is no evidence that these differences are clinically significant.

5.3 Preclinical safety data

Preclinical data did not detect any specific damage to humans on the basis of traditional studies involving single dose toxicity, recurrent dose toxicity, carcinogenic potential and reproductive / developmental toxicity.

Levofloxacin did not cause any impairment in fertility or reproductive performance in rats and the only effect on fetus is growth retardation due to maternal toxicity.

Levofloxacin did not cause gene mutation in bacterial or mammalian cells, but caused Chinese hamster's lung cells in vitro chromosome breakage. These effects can be attributed to the inhibition of topoisomerase II. In vivo tests (micronucleus, sister chromatid exchange, unplanned DNA synthesis, dominant lethal tests) showed no genotoxic potential.

Studies in mice have shown that levofloxacin has phototoxic activity only in very high doses. Levofloxacin did not show genotoxic potential in the determination of photomutagenity and reduced tumor growth in a photocarcinogenicity study.

Levofloxacin, like other fluoroquinolones, showed an effect on cartilage (peel and cavity formation) in rats and dogs. These effects were more pronounced in young animals.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Crospovidone

Hydroxypropylmethyl cellulose

Sodium stearyl fumarate

Opadry White*

* Polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep in room temperature under 25°C.

6.5. Nature and contents of container

In box, in PVC / PVDC aluminum foil blister packaging 7 film tablets

7. MARKETING AUTHORISATION HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.

Oğuzlar Mah. 1370. sok. No: 7/3

06520 Balgat-ANKARA

Phone: 0 312 287 74 10

8. MARKETING AUTHORISATION NUMBER

216/4

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Date of first authorisation: 29.05.2008

License renewal date:

9. DATE OF REVISION OF THE TEXT

22/04/2019