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

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

1. NAME OF THE MEDICINAL PRODUCT

RAVIVO 500 mg / 100 ml Vial Containing IV Infusion Solution

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:

100 ml infusion solution,

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

Excipients:

Sodium chloride		900 mg
Sodium hydroxide	q.s.(pH: 4,8)	4,5 mg

Please refer to 6.1 for other excipients.

3. PHARMACEUTICAL FORM

Solution for Infusion, IV

Transparent homogenous solution with light yellow color

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Pneumonia, obtained in society

Caused by Staphylococcus aureus, Streptococcus pneumoniae (including penicillin resistant strains of which MIC value for penicillin ≥ 2 µg/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 veya 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*

- Hospital acquired pneumonia

Staphylococcus aureus, Pseudomonas aeruginosa, Serratia marcescens, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Haemophilus influenzae or *Streptococcus pneumoniae.* If the reported or suspected pathogen is Pseudomonas aeruginosa, combined therapy with an anti-pseudomonal β-lactam is recommended.

- 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 IV might be administered once or twice per day in form of slow intravenous infusions (infusion of at least 60 minutes). Dosage is adjusted in connection with type, severity of infection, and sensitivity of possible active pathogen. Depending on the status of the patient, it is possible to pass to oral administration with RAVIVO 250 or 500 mg film coated tablet a few days after initial IV application. As oral and parenteral forms are bioequivalent, it is possible to use the same dosage in both forms.

Posology:

RAVİVO 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	**Usage Period** (according to severity of
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
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
Hospital acquired pneumonia	Daily single dose 750 mg	10-14 days
Anthrax inhalation	Daily single dose 500 mg	8 weeks

** Dosage increase should be considered for severe infection cases.*

Method of administration:

RAVİVO is only administered by slow intravenous infusion. The administration can be done once daily or twice a day. Infusion period should be 60 minutes for 500 mg RAVIVO I.V. solution (See Section 4.4). In connection with the status of the patient, it is possible to pass to

oral application from initial intravenous application with the same dosage within a few days.
For incompatibilities, see Section 6.2.

Treatment period

Treatment period depends on course of the disease (refer to the table above). In general, like in all antibiotic treatments, RAVIVO IV 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	*then:* 125 mg/24 hours	*then:* 250 mg/24 hours	*then:* 250 mg/12 hours
19-10 ml/min.	*then:* 125 mg/48 hours	*then:* 125 mg/24 hours	*then:* 125 mg/12 hours
< 10ml / min (along with hemodialysis and continual ambulatory	*then:* 125 mg/48 hours	*then:* 125 mg/24 hours	*then:* 125 mg/24 hours

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

Liver failure:

Levofloksasin 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 IV 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 IV (levofloxacine) should not be used:

- Patients, known to be very sensitive against levofloxacine or any agent within the compound of RAVIVO IV 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 IV, have been associated with potentially irreversible serious adverse reactions that can lead to disability. Common advers reactions are musculosketal 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 IV. Patients of all age groups or those who do not have pre-existing risk factors, experience these adverse reactions.

RAVİVO should be discontinued immediately if any signs or symptoms of any serious adverse reaction occur. In addition, the use of fluoroquinolones, including RAVIVO IV, 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 IV 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,busing levofloxacin in the treatment of MRSA infections known or suspected not recommended unless confirmed by laboratory test organism levofloxacin sensitivity.

Patients susceptible to convulsions :

As with other quinolones RAVIVO I.V. infusion solution, in patients with a history of epilepsy contraindicated.

In patients with a previous central nervous system lesion who are susceptible to convulsions, in patients who are taking fenbufen or similar non-steroidal antiinflammatory drugs and in patients taking drugs that lower the threshold of cerebral convulsions should be used with

extreme caution (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 RAVİVO 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, RAVİVO 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, prevent bowel movements drugs 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 who were taking corticosteroids and used 1000 mg daily. If RAVIVO IV 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 IV 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 immediately contact the doctor.

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)
Patients and women may be more sensitive to drugs that prolong the QTc interval at an advanced age. Therefore, for fluoroquinolones, including levofloxacin, caution should be exercised when used in this patient group.

Dysglycemia:
As with other quinolones generally oral hypoglycemic agents (e. g. Glibenclamide) or insulin has been reported that diabetic patients treated with hypoglycaemia. Hypoglycemic coma have been reported. Diabetes is recommended careful monitoring of blood glucose in patients. (See Section 4.8)

The exacerbation of myasthenia gravis:
Fluoroquinolones, including levofloxacin have neuromuscular blocking activity to and can exacerbate muscle weakness in myasthenia gravis patients. Fluoroquinolone use in patients with myasthenia gravis, lung failure requiring ventilatory support and post-marketing serious adverse events, including death, have been associated with fluoroquinolone. Patients with myasthenia gravis history should be avoided from use fluoroquinolone.

Patients with renal failure :
Levofloxacin is mainly excreted through the kidneys. In patients with renal failure should be set the dose of RAVIVO I.V. infusion solution (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 if appropriate treatment should be applied.

Glucose-6-phosphate dehydrogenase deficiency Patients:

Patients with latent or actual defect in glucose-6-phosphate dehydrogenase activity may increase the tendency 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, has been reported in patients using fluoroquinolone, including levofloxacin. In order to prevent the development of irreversible disorders, if the patient experiences symptoms of neuropathy, the use of levofloxacin should be discontinued.

Inhalation anthrax:

Use in humans, in vitro Bacillus anthrasis susceptibility data is based on, experimental data in animals and limited data in humans. The attending physician should consult the national and / or international consensus documents on the treatment of anthrax.

The duration of infusion:

During this time, the patient should be observed. With RAVİVO infusion, tachycardia and temporarily blood pressure decrease can be reduced , and in rare cases blood circulation decreases with circulatory collapse. If a significant decrease in blood pressure is observed during infusion of levofloxacin (l-isomer of ofloxacin), the infusion should be discontinued immediately.

Sodium content:
This medicinal product contains 15.49 mmol (356.42 mg) sodium per 100 ml dose. This should be considered for patients on a controlled sodium diet.

Patients treated with vitamin K antagonists:
Against the possibility of increase of coagulation tests (PT / INR) and/or increased bleeding, if RAVİVO and vitamin K antagonists (eg warfarin) are used together, follow-up with coagulation tests is required (see Section 4.5).

Psychotic reactions:
Including levofloxacin, have been reported in patients receiving quinolones have developed psychotic reactions. In very rare cases, after a single dose of levofloxacin, suicidal thoughts and self-endangering behaviors were observed (See Section 4.8). If patients develop such reactions, levofloxacin should be discontinued and appropriate measures taken. Caution should be exercised if levofloxacin should be used in patients with psychotic disorders 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, a false positive result may be obtained during the detection of opiate in the urine. This result may need to be verified using more original methods.

Levofloxacin may suppress Mucobacterium tuberculosis proliferation and this may lead to a false negative result in the bacteriological diagnosis of tuberculosis.

This medicinal product contains 15.5 mmol (or 356.6 mg) of sodium per dose. This should be considered for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Teophiline, 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. Levofloxacin together with a vitamin K antagonist (eg, warfarin) may cause severe increases in coagulation tests (PT / INR) and / or bleeding.

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).

In 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.

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

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. RAVİVO 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. It cannot be excluded that there is a risk for breastfeeding child due to physicochemical and pharmacological / toxicological data. In experimental studies with fluoroquinolones, RAVİVO 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 RAVİVO 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 RAVİVO 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1.000 to < 1/100); rare (≥ 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 sorted by 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-destructive behaviors, including suicidal thoughts and suicide attempts

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 cardia 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

Common: phlebitis

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.

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

In patients with primary underlying severe disease, cases of acute hepatic failure which are sometimes fatal with levofloxacin have been reported (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
Common: reactions at the injection site (pain, redness)
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 I.V. 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

Pharmacoterapeutic group: quinolone antibacterials, fluoroquinolones

ATC code: J01MA12

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

Mechanism of Action

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

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*, Enterecoccus* spp, *Listeria monocytogenes,* Koagülaz negatif stafilokoklar (sensitive to methicillin), *Staphylococcus aureus* (sensitive to methicillin)*, *Staphylococcus epidermidis* (sensitive to methicillin), *Staphylococcus saprophyticus,* C and G group streptococcus, *Streptococcus agalactiae, Streptococcus pneumoniae* (sensitive to penicillin / intermediate level resistant / resistant)*, *Streptococcus pyogenes**, Viridans streptococcus (resistant / sensitive to penicillin)

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** (resistant / sensitive to ampicillin), *Haemophilus parainfluenzae*, Helicobacter pylori, Klebsiella oxytoca, Klebsiella pneumoniae*, Klebsiella* spp, *Moraxella catarrhalis* (beta-lactamase-positive / beta-lactamase-negative)*, *Morganella morganii*, Neisseria gonorrhoeae* (producing penicillinase / not producing penicillinase), *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 neusochemical 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, there is no cross-resistance between levofloxacin and other classes of antibacterial drugs.

Limit Value

The recommended MIC cutoff 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 ik mg / l).

EUCAST clinical MIC limit values for levofloxacin (version2.0,2012-01-04):

Pathogen	**Sensitive**	**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	≤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
Limit values that is not intrinsic to species	≤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. Where necessary, expert advice should be sought for the prevalence of local resistance in cases where the use of the drug is questioned at least in some infections.

5.2 Pharmacokinetic properties

General properties

Absorption:

After oral administration of levofloxacin is rapidly and almost completely absorbed by obtaining peak plasma concentrations in 1-2 hours (After single dose of 500 mg levofloxacin followed by Cmax: 5.2 /- 1.2 microg / ml). The absolute bioavailability is 99-100%. Levofloxacin has linear pharmacokinetic properties in the range of 50 to 1000 mg.

It reach a steady state in 48 hours after taking 500 mg one or two doses per day.

The table showing the peak and pit plasma concentrations on day 10 of the multiple oral or IV 500 mg dose administered daily or once in two days is as follows:

PK Parameter (mean ±SD)	**500 mg multiple-dose management**			
	Single dose/day		**Two doses / day**	
	500 mg oral	**500 mg IV***	**500 mg oral**	**500 mg IV**
Peak plasma concentration(mcg/ml)	5.7 ± 1.4	6.4 ± 0.8	7.8 ± 1.1	7.9 ±1.1
Pit plasma concentration(mcg/ml)	0.5 ± 0.2	0.6 ± 0.2	3.0 ±0.9	2.3 ± 0.5

* Infusion period for 500 mg IV is 60 minutes.

There is a small effect of food on the absorption of levofloxacin.

Distribution:

After administration of a single dose and repeated doses of 500 mg and 750 mg, the average dispersion volume of levofloxacin distributed widely in the body tissues is about 100 l. Approximately 30-40% of levofloxacin is bound to serum proteins.

Transfer to tissues and body fluids:

Penetration to Bronchial Mucosa, Epithelial Mucus Fluid and Alveao Macrophages

After 500 mg single oral administration, the maximum concentrations in bronchial mucosa and epithelial mucus fluid were 8.3 mcg / g and 10.9 mcg / 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.

Following oral administration of 500 mg and 750 mg for 5 days, the average concentrations in the epithelial mucus fluid after 4 hours of administration were 9.94 microg / ml and 22.12 microg / ml, respectively. The alveolar macrophages were 97.9 microg / ml and 105.1 microg / ml, respectively.

Penetration into Lung Tissue

The maximum concentration of levofloxacin in lung tissue after an oral dose of 500 mg was 11.3 microg / g. 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

After 3 to 4 hours of 500 mg daily or twice in a day for 3 days, the maximum concentration of levofloxacin in the bulla fluid was 4 and 6.7 microg / ml, respectively, and the bulla / plasma ratio was approximately 1.

Distribution of Bone Tissue

Levofloxacin penetrates well in the proximal and distal femur, with a penetration rate of between 0.1 and 3. The maximum concentration of levofloxacin in the spongios proximal femur after 500 mg of oral dose was approximately 15.1 microg / g 2 hours after administration.

Cerebro-Spinal Fluid Penetration

Levofloxacin transition to cerebrospinal fluid is low.

Prostate tissue distribution

After administration oral 500 mg levofloxacin 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.

Biotransformation:

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

Elimination:

Levofloxacin is eliminated from plasma relatively slowly following oral and intravenous administration (t½: 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, suggesting 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. As kidney function decreases, elimination and clearance from kidneys decreases and the elimination half-life is prolonged, as shown in the table below:

Clcr [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 Chinese hamster caused chromosome breakage in lung cells. 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 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

Sodium chloride

Sodium hydroxide, (ad. pH= 4.8)

Hydrochloric acid

Water for injection

(Sodium concentration: 15,49 mmol (356,42 mg) / 100 ml)

6.2 Incompatibilities

RAVIVO IV is compatible with below listed infusion solutions:

0.9 % sodium chloride solution

5 % dextrose solution

2.5% dextrose, combination solutions (amino acids, carbohydrates, electrolytes) prepared for parenteral nutrition in Ringer's solution,

RAVIVO IV should not be mixed with heparin or alkali solutions (e. g. sodium hydrogen carbonate).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep in room temperature under 25°C and in its original package. Keep away from light. After unpacking, the durability in room light is 3 days.

6.5. Nature and contents of container

In the box, the solution in a colorless glass vial sealed with a metal hood on the flip-off lid and rubber stopper, 1 piece.

6.6 Special precautions for disposal and other handling

Unused products or waste materials must be disposed of in accordance with the ın Regulation on Control of Medical Wastes and Regulation on Control of Packaging and Packaging Wastes.

7. MARKETING AUTHORISATION HOLDER

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22/04/2019