SUMMARY OF PRODUCT CHARACTERISTICS

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

Fluoroquinolones, including RAVIVO, can cause disabling and irreversible adverse reactions such as:

- o Tendonitis and tendon rupture
- o Peripheral neuropathy
- o Central nervous system effects

In patients with any of these reactions, use of RAVIVO should be discontinued immediately and fluoroquinolone should be avoided.

Fluoroquinolones, including RAVIVO, may exacerbate muscle weakness in patients with myasthenia gravis. Use of RAVIVO should be avoided in patients with a known history of myasthenia gravis.

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

- o Acute bacterial sinusitis
- o Uncomplicated urinary infection
- o Acute bacterial exacerbation of chronic bronchitis

1. NAME OF THE MEDICINAL PRODUCT

RAVIVO 750 mg film coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Levofloxacin hemyhydrate 768.69 mg

(equivalent to 750 mg levofloxacin)

Excipients:

Sodium stearyl fumarate 11.14 mg

See Section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Film coated tablet

White, oblong, notched, film coated tablets

4. CLINICAL PROPERTIES

4.1.Therapeutic indications

In acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary infections should not be used because of the risk of serious side effects if alternative treatment options are available. In addition, sensitivity should be demonstrated by antibiogram in urinary infections.

RAVIVO is indicated for the treatment of infections in adults, which are caused by susceptible microorganisms.

- **Community-acquired pneumonia:**

Methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae (including multi-drug resistant strains), Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis, Klebsiella pneumoniae, Legionella pneumophila, Chlamydia pneumoniae and Mycoplasma pneumoniae are the causative agents of infection.

- **Hospital-acquired (nosocomial) pneumonia:**

Hospital-acquired pneumonia caused by methicillin-sensitive Staphylococcus aureus, Pseudomonas aeuroginosa, Serratia marcensens, Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae or Streptococcus pneumonia.

If the suspected pathogen is Pseudomonas aeuroginosa, combined therapy with an anti-pseudomonal ß-lactam is recommended.

- **Acute exacerbation of chronic bronchitis:**

Infections caused by methicillin-sensitive Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae or Moraxella catarrhalis.

- **Acute bacterial sinusitis:**

Infections caused by Streptococcus pneumoniae, Haemophilus influenzae or Moraxella catarrhalis strains.

- **Uncomplicated urinary tract infections:**

Infections caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis or Staphylococcus saprophyticus.

- **Complicated urinary tract infections**

Infections caused by Enterococcus faecalis, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae or Proteus mirabilis or Pseudomonas aeruginosa.

- **Chronic bacterial prostatitis:**

Chronic bacterial prostatitis caused by Escherichia coli, Enterococcus faecalis or methicillin-sensitive Staphylococcus epidermidis.

- **Acute pyelonephritis**

In infections of Escherichia coli origin, including associated bacteremia.

- **Uncomplicated skin and soft tissue infections**

In infections caused by methicillin-sensitive Staphylococcus aureus or Streptococcus pyogenes.

- **Complicated skin and soft tissue infections:**

In infections caused by methicillin-sensitive Staphylococcus aureus, Enterococcus faecalis, Streptococcus pyogenes or Proteus mirabilis.

- **Inhaled Anthrax (after exposure):**

Inhaled anthrax treatment (after exposure) to reduce the frequency or progression of the disease following exposure to contaminated air with Bacillus anthracis. There is no study showing the safety of RAVIVO in adults over 28 days.

4.2. Posology and administration route

Posology / frequency and duration of administration:

RAVIVO is recommended as a single dose per day. The dosage is adjusted depending on the type, severity of the infection and the sensitivity of the causative pathogen.

The duration of treatment varies depending on the course of the disease. As with all antibiotic treatments in general, RAVIVO treatment should be continued for 48-72 hours after the patient is afebrile or bacterial eradication is achieved.

RAVIVO is recommended to be administered in the following doses:

Dosage in patients with normal renal function (creatinine clearance ≥ 50mL / min):

Indication	**Daily dosage (according to severity of infection)**	**Duration of treatment**
Community-acquired pneumonia	Daily single dose 500 mg Daily single dose 750 mg	7-14 days 5 days
Hospital-acquired (nosocomial) pneumonia	Daily single dose 750 mg	7-14 days
Acute exacerbation of chronic bronchitis	Daily single dose 500 mg	7 days
Acute bacterial sinusitis	Daily single dose 500 mg Daily single dose 750 mg	10-14 days 5 days
Uncomplicated urinary tract infections	Daily single dose 250 mg	3 days
Complicated urinary tract infections	Daily single dose 250 mg Daily single dose 750 mg	10 days 5 days

Chronic bacterial prostatitis	Daily single dose 500 mg	28 days
Acute pyelonephritis	Daily single dose 250 mg Daily single dose 750 mg	10 days 5 days
Uncomplicated skin and soft tissue infections	Daily single dose 500 mg	7-10 days
Complicated skin and soft tissue infections	Daily single dose 750 mg	7-14 days
Inhaled Anthrax (after exposure)	Daily single dose 500 mg	60 days

Administration route:

It is taken by oral administration.

RAVIVO should be taken with sufficient liquid without chewing. For dose adjustment, tablets may be divided as required. Tablets can be taken during meals or between meals. RAVIVO should be taken 2 hours before the administration of iron salts, antacids and sucralfate to prevent reduced absorption (see Section 4.5.Interactions with other medicinal products and other forms of interaction).

Additional information about special populations

Kidney failure:

Dosage in patients with renal insufficiency (creatinine clearance <50 ml / min):

Recommended dose every 24 hours for normal renal function	Creatinine clearance 20-49 ml/min	Creatinine clearance 10-19 ml/min	Hemodialysis or Chronic Ambulatory Peritoneal Dialysis
750 mg	750 mg every 48 hours	Initial dose 750 mg, then every 48 hour 500 mg	Initial dose 750 mg, then every 48 hour 500 mg
500 mg	Initial dose 500mg, then every 24 hour 250 mg	Initial dose 500mg, then every 48 hour 250 mg	Initial dose 500mg, then every 48 hour 250 mg
250 mg	Dose adjustment is not required	250 mg every 48 hours. No dose adjustment is required for uncomplicated urinary tract infection.	There is no data about dose adjustment

Liver failure:

RAVIVO is metabolized in the liver in very low amounts and is excreted mainly through the kidneys. Therefore, dosage adjustment is not necessary in liver failure.

Pediatric population:

RAVIVO should not be used in pediatric patients and patients under 18 years of age.

Geriatric population:

Dosage adjustment is not necessary if renal function is sufficient in elderly patients.

4.3. Contraindications

RAVIVO is contraindicated in the following cases.

- Patients known to have hypersensitivity to levofloxacin, quinolone group other antibacterial agents or any of the excipients present in its composition
- In patients with epilepsy
- Patients with a history of tendon disorders known to develop due to the use of an fluoroquinolone group antibacterial
- Children under the age of 18
- During pregnancy
- During breastfeeding

4.4. Special warnings and precautions

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

Fluoroquinolones, including RAVIVO, have been associated with serious irreversible and potentially irreversible adverse reactions. Common adverse reactions include musculoskeletal and peripheral nervous system (tendonitis, tendon rupture, tendon swelling or inflammation, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, swelling of joints), arthalgia, myalgia, peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendency, insomnia, severe headache, and confusion) (see section 4.8).

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

In the event of the first signs or symptoms of any serious adverse reactions, RAVIVO should be discontinued immediately. Furthermore, the use of fluoroquinolones, including RAVIVO, should be avoided in patients experiencing any of these serious adverse reactions in connection with fluoroquinolones.

In patients with convulsions

Caution should be exercised when administering levofloxacin to patients with a history of epilepsy and a tendency to convulsion, that is to say a central nervous system lesion, with fenbufen or similar nonsteroidal anti-inflammatory drugs or with a drug known to lower the brain convulsion threshold, such as theophylline.

Convulsions and toxic psychosis have been reported in patients receiving quinolone, including RAVIVO. Quinolones may cause increased intracranial pressure and CNS stimulation (such as tremor, restlessness, anxiety, confusion, hallucination, paranoia, depression, nightmares, insomnia, and rarely suicidal thoughts and attempts).

As with other quinolones, RAVIVO should be used with caution in people with known CNS disease.

Psychotic reactions

Psychotic reactions have been reported in patients taking quinolones, including levofloxacin. In very rare cases, after a single dose of levofloxacin, this sometimes progresses to personality change and suicide. Levofloxacin should be discontinued and appropriate treatment initiated in patients with these reactions. Levofloxacin should be used with caution in psychotic patients or in patients with a psychiatric history.

Peripheral Neuropathy

Sensory or sensorimotor peripheral neuropathy has been reported in patients receiving fluoroquinolone, including levofloxacin. Levofloxacin should be discontinued to prevent the development of irreversible conditions in patients with symptoms of neuropathy.

Hypersensitivity

As with other quinolones, severe and sometimes fatal hypersensitivity and / or anaphylactic reactions have been reported with RAVIVO. Use of RAVIVO should be discontinued immediately if any signs of skin rash or hypersensitivity occur.

Diseases due to Clostridium difficile

Pseudomembranous enterocolitis has been reported with almost all antibacterial agents, including RAVIVO. Treatment with antibacterial agents changes the normal colon flora, causing excessive proliferation of clostridia. Studies have shown that the toxin produced by Clostridium difficile is the primary cause of antibiotic-associated colitis. In mild cases, cessation of the drug is sufficient, and in moderate to severe cases, fluid, electrolyte, protein supplementation and Clostridium difficile may require an effective antibacterial agent.

Tendinitis

During the treatment using levofloxacin belonging to fluoroquinolone group, cases of tendinitis have rarely been observed. Tendonitis increases with corticosteroid use and may occur 48 hours after treatment is started. Levofloxacin therapy should be discontinued in patients suspected of tendonitis and appropriate treatment for tendinitis (to neutralize the affected tendon) should be initiated.

Tendon rupture

Tendon ruptures that may require surgical treatment or may cause prolonged disability have been reported in patients receiving quinolone treatment, including RAVIVO. Post-marketing follow-up studies have reported an increased risk, especially in elderly and concomitant patients receiving corticosteroids. Tendon rupture may develop during or after treatment with quinolones, including RAVIVO. RAVIVO should be discontinued if pain, inflammation or rupture develops in the patient's tendon.

In patients with Glucose-6-phosphate dehydrogenase activity deficiency

Since hemolytic reactions with quinolone group antibacterials have been reported in these patients, caution should be careful in the use of levofloxacin.

Kidney failure

Although RAVIVO is more soluble than other quinolones, patients should be hydrated sufficiently to prevent condensation in the urine.

RAVIVO should be used with caution in case of renal failure. dose adjustment is required in patients with creatinine clearance <50 mL / min. (see section 4.2 Posology / frequency and duration of administration)

Liver disorders

Levofloxacin has been reported, especially in patients with severe disease (eg sepsis), to life-threatening hepatic failure and hepatic necrosis. If symptoms and signs of liver disease such as anorexia, jaundice, dark urine, pruritis or tender abdomen develop, patients should be advised to stop treatment and notify their doctor.

Prevention of photosensitization

Moderate to serious phototoxicity reactions have been observed in patients using this class of medication when exposed to direct sunlight. During levofloxacin treatment, patients should avoid excessive exposure to severe sunlight or artificial ultraviolet rays such as solariums. However, in clinical studies with RAVIVO, phototoxicity was observed in less than 0.1% of patients. If phototoxicity occurs, the drug should be discontinued.

Blood Glucose Level

As with other quinolones, impaired blood glucose levels, symptomatic hyper or hypoglycemia have been observed in diabetic patients, particularly in patients receiving concomitant oral hypoglycemic agents (such as glyburide or glibenclamide) or insulin. In a patient receiving RAVIVO if hypoglycemia occurs, RAVIVO should be discontinued immediately. Blood glucose should be monitored in patients with diabetes.

QT prolongation

RAVIVO may cause long QT syndrome / Torsades de Pointes. Therefore, it should not be used in patients with diagnosed or suspected congenital prolonged QT syndrome or Torsades de Pointes.

In patients treated with vitamin K antagonists

In patients who are using levofloxacin and vitamin K antagonists together, the patient's coagulation tests should be monitored due to increased coagulation tests parameters and bleeding.

Exacerbation of Myasthenia Gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in patients with myasthenia gravis. In patients with myasthenia gravis using fluoroquinolone, severe post-marketing adverse events, including the need for ventilator support and death, have been associated with fluoroquinolone. Patients with a history of myasthenia gravis should avoid using fluoroquinolone.

General

As with any powerful antimicrobial drug, periodic evaluation of organ system (renal, hepatic and hematopoietic) functions is recommended.

Other

Oral and intravenous administration of RAVIVO in immature rats and dogs increased the incidence of osteochondrosis. Other fluoroquinolones have also produced similar erosions in the load bearing joints and other signs of arthropathy in different immature animal species.

This medicinal product contains less than 1 mmol (23 mg) of sodium per tablet; no sodium-related side effects are expected at this dose.

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

Iron salts, zinc-containing multivitamins, magnesium or aluminum-containing antacids and sucralfate:

When RAVIVO is taken together with iron salts, zinc-containing multivitamins, magnesium or aluminum-containing antacids, and sucralfate, for cause the absorption of RAVIVO is markedly reduced, these drugs should be administered at least two hours before or two hours after RAVIVO administration.

Theophylline:

No interactions between RAVIVO and theophylline have been reported in clinical trials. Theophylline levels should be monitored in combination with RAVIVO, since theophylline levels increase with other quinolones.

K vitamins antagonists and warfarin:

Coagulation tests should be carefully monitored in patients treated with vitamin K antagonists. In patients treated with levofloxacin and a vitamin K antagonist (such as warfarin) severe increases have been reported in clotting tests (PT / INR) and / or bleeding.

No significant interaction between RAVIVO and warfarin has been reported. However, during concomitant use of RAVIVO warfarin, patients should be monitored for prothrombin time and signs of bleeding.

Cyclosporine:

Cyclosporine half-life increases by 33% when levofloxacin in combination with cyclosporine is used.

This clinically insignificant increase does not require adjustment of the cyclosporine dose.

Digoxin:

No significant interaction has been reported during concomitant use of RAVIVO and digoxin. No dose adjustment is required for concomitant use.

Probenecid and cimetidine:

During the concomitant use of RAVIVO with probenecid or cimetidine, RAVIVO's AUC (Area Under Curve) and half-life were 27-38% and 30% higher, and creatinine clearance was 21-35% lower, respectively. Although these differences are statistically significant, RAVIVO does not require dose adjustment when combined with probenecid and cimetidine. Caution should be exercised in patients with renal insufficiency.

Non-steroidal anti-inflammatory drugs:

When a nonsteroidal anti-inflammatory drug is used in combination with a quinolone group antibiotic, including RAVIVO, the risk of falls in the brain convulsion threshold may be increased.

Antidiabetic drugs:

Hyperglycemia and hypoglycemia have been reported during concomitant use of quinolones and antidiabetic drugs. Therefore, blood sugar levels should be monitored in concomitant use.

Drugs that prolong the QT interval:

Arrhythmia may occur when used in combination with Class IA and Class III antiarrhythmic drugs, tricyclic antidepressants, erythromycin and cisapride.

Interactions with laboratory or diagnostic tests:

Certain quinolones, including levofloxacin, can lead to false-positive results in narcotic drug determination in urine by immunoassay tests.

Additional information on special populations

Renal / liver failure:

No interaction studies have been conducted with RAVIVO in patients with renal or hepatic impairment.

Pediatric population:

No interaction studies have been conducted with RAVIVO in pediatric patients.

4.6. Pregnancy and lactation

General Advise:

Pregnancy cathegory: C

Women with childbearing potential / Birth control (Contraception)

There is insufficient data on the use of RAVIVO in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Pregnancy

RAVIVO should not be used during pregnancy.

Lactation period

RAVIVO was not measured in breast milk. Based on data on ofloxacin, it can be predicted that RAVIVO may also pass into breast milk. RAVIVO tablets should not be used during lactation.

Reproductive ability / Fertility

The toxicity potential of RAVIVO on fertility, embryotoxicity and peri / post natal functions has been studied with oral administration on rats, as well as on the potential of embryotoxicity on rabbits.

RAVIVO had no effect on fertility. Intrauterine growth retardation was observed on the fetus. The teratogenic effect was not observed.

4.7. Effects on ability to drive and use machines

Caution should be exercised when driving and operating machinery since RAVIVO can cause neurological side effects such as dizziness and daze.

4.8. Undesirable effects

The frequency of adverse reactions is as follows:

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 (can not be estimated from the available data).

Infections and infestations

Uncommon: Fungal infection (and proliferation of other resistant microorganisms)

Blood and lymphatic diseases

Uncommon: Leukopenia, eosinophilia

Rare: Thrombocytopenia, neutropenia

Very rare: Agranulocytosis
Unknown: Pancytopenia, hemolytic anemia

Diseases of the immune system
Very rare: Anaphylactic shock (anaphylactic and anaphylactoid reactions may sometimes develop following the first dose)
Unknown: Hypersensitivity

Metabolism and nutritional diseases
Uncommon: Anoxia
Very rare: Hypoglycemia (especially in diabetic patients)

Psychiatric diseases
Rarely: Insomnia, irritability
Rare: Psychotic disorder, depression, confusion, agitation, anxiety
Very rare: suicidal thoughts or behavior, including hallucinations, self-harm and psychotic reactions.

Diseases of the nervous system
Uncommon: dizziness, headache, dizziness
Rare: Convulsion, tremor, paresthesia
Very rare: Sensory or sensory-motor peripheral neuropathy, taste and odor disorders
Eye disorders
Very rare: Vision disorders

Ear and inner ear diseases
Uncommon: Vertigo
Very rare: Hearing disorders
Unknown: Tinnitus

Cardiac diseases
Rare: Tachycardia
Unknown: Extension of QT interval on electrocardiogram

Vascular diseases

Rare: Hypotension

Respiratory system, chest diseases and mediastinal disorders

Rare: Bronchospasm, shortness of breath

Very rare: Allergic pneumonia

Gastrointestinal diseases

Common: Diarrhea, nausea

Uncommon: Vomiting, abdominal pain, dyspepsia, bloating, constipation

Rare: Bloody diarrhea (may be a sign of an enterocolitis, including very rare pseudomembranous colitis.)

Hepatobiliary diseases:

Common: Increased liver enzyme levels (ALT, AST, alkaline phosphatase, GGT)

Uncommon: Increase in blood bilirubin levels

Very rare: Hepatitis

Unknown: Jaundice and severe liver damage, including acute liver failure, have been reported primarily in patients with serious illnesses prior to treatment.

Skin and subcutaneous tissue diseases:

Uncommon: Skin rash, itching

Rare : Urticaria

Very rare: Angioneurotic edema, photosensitivity reactions

Unknown: Toxic epidermel necrosis, Stevens-Johnson syndrome, erythema multiforme, excessive sweating (Mucocutaneous reactions sometimes occur following the first dose)

Musculoskeletal disorders, connective tissue and bone diseases

Rare: tendon disorders including tendinitis (eg Achilles tendon), joint pain, muscle pain

Very rare: exacerbation of myasthenia gravis, tendon rupture (this undesirable effect may occur within the first 48 hours of treatment and bilaterally), muscle weakness is important in patients with myasthenia gravis.

Unknown: Rhabdomyolysis

Kidney and urinary system diseases

Uncommon: Increased serum creatinine

Very rare: Acute renal failure (eg due to interstitial nephritis)

General disorders and application area diseases

Uncommon: Asthenia

Very rare: Fever

None known: Pain (including back, chest and extremity pain)

Other adverse effects reported due to fluoroquinolone use;

• extrapyramidal symptoms and other muscle coordination disorders,

• hypersensitivity vasculitis,

• Porphyria attacks in patients with porphyria.

Additional information on special populations

No interaction studies have been conducted.

Pediatric population:

Safety and efficacy have not been established in pediatric patients and adolescents under 18 years of age.

Quinolones, including levofloxacin, caused arthropathy and osteochondrosis in juvenile animals of various species.

4.9. Overdose and treatments

Based on animal toxicity studies or clinical pharmacology, RAVIVO should be expected to show signs of acute overdose, such as confusion, dizziness, loss of consciousness and convulsive contractions, as well as central nervous system symptoms, such as nausea and mucosal erosion.

In case of acute overdose of RAVIVO, gastric lavage should be considered, symptomatic treatment should be performed and ECG should be monitored due to the possibility of prolongation of QT interval. Antacids may be administered to protect the gastric mucosa. Hemodialysis, peritoneal dialysis or continuous ambulatory peritoneal dialysis is not effective in removing RAVIVO from the body.

RAVIVO has no specific antidote.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials

ATC Code: J01MA12

The bactericidal effect of RAVIVO occurs, as in other fluoroquinolones, by inhibiting the deoxyribonucleic acid (DNA) gyrase enzyme of bacteria.

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

RAVIVO has been shown to be effective against the following pathogens by in vitro studies.

Gram positive aerobes: Enterococcus faecalis * (many strains are only moderately sensitive), Staphylococcus aureus * (methicillin sensitive strains) *, Staphylococcus epidermadis * (methicillin sensitive), Staphylococcus saprophyticus *, Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP[#]] , Streptococcus pyogenes*. Staphylococcus haemolyticus, Streptococcus (Group C / F), Streptococcus (Group G), Streptococcus agalactiae, Streptococcus shafts, Viridans group streptococci

#MDRSP (multidrug resistant Streptococcus pneumoniae) isolates include penicillin (MIC 2µg / ml), 2nd generation cephalosporins, macrolides, tetracyclines, and strains that are resistant to 2 or more antibiotics from trimethoprim sulfamethoxazole.

Gram-negative aerobes : Enterobacter cloacae*, Escherichia coli*, Haemophilus influenzae*, H. parainfluenzae*, Klebsiella pneumoniae*, Legionella pneumophilia*, Moraxella catarrhalis, Proteus mirabilis*, Pseudomonas aeruginosa*, Serratia marcescens*, Acinetobacter baumannii, Acinetobacter lwoffi, Bordetella pertussis, Citrobacter (diversus) koseri, itrobacter freundii, Enterobacter aerogenes, Enterobacter sakazakii, Klebsiella oxytoca, Morganella morganii, Pantoea (Enterobacter) agglamerans, Proteus vulgaris, Providencia rettgeri, Providencia stuartii, Pseudomonas fluorescens.

Anaerobes bacteries: Bacteroides fragilis, Clostridium perfringens, Peptostreptococcus

Other microorganisms: Chlamydia pneumoniae*, Chlamydia psittaci, Legionella pneumophilla*, Mycoplasma pneumoniae*.

The efficacy of RAIVO against Bacillus anthracis has been demonstrated both in vitro and in vivo.

* Clinical efficacy has been proven in clinical research.

5.2.Pharmacokinetic properties

General features:

There is no significant difference in the pharmacokinetics of oral and intravenous administration of RAVIVO; therefore, oral administration can be switched from one to another.

Absorbation:

Orally administered RAVIVO is rapidly and completely absorbed from the gastrointestinal tract. Serum peak concentrations are reached within 1 hour after oral administration. Stady-state concentrations are reached 48 hours after the administration of 500 mg or 750 mg of RAVIVO. The absolute bioavailability is about 99%. RAVIVO follows a linear pharmacokinetics in the dose range of 50-600 mg. Taking RAVIVO with food reduces peak blood concentrations by 14% and delays the time to reach peak blood concentrations by about 1 hour. However, RAVIVO can be administered independently of meals.

Distribution:

The average volume of distribution after administration of single doses of RAVIVO and multiple doses of 500 or 750 mg is 74-112 L. RAVIVO is widely distributed in body tissues. RAVIVO also penetrates well into lung tissue and after single dose administration, lung tissue concentrations reach 2-5 times their plasma concentration and bind to approximately 24-38% of RAVIVO serum proteins and are mainly bound to albumin.

Metabolism:

RAVIVO is metabolized only to a small extent and is mainly present in the urine unchanged. Approximately 87% of the dose administered after oral administration is detected as unchanged drug in the urine within 48 hours. Less than 5% of the administered dose is detected in the urine as metabolites.

Elimination:

RAVIVO is excreted in the urine as a largely unchanged drug. The mean terminal plasma half-life of RAVIVO, administered orally or intravenously in single or multiple doses, was between 6-8 hours. The mean total body clearance and renal clearance were 144-226 mL / min and 96 mL / min, respectively.

Linearity / Non-Linearity:

Single or multiple oral or i.v. It shows a predictable linear pharmacokinetics in RAVIVO.

Characteristics of patients:

Pharmacokinetics in elderly patients:

There was no significant difference in the pharmacokinetics of RAVIVO in elderly and young patients. The dose of RAVIVO alone does not need to be adjusted for age.

Pharmacokinetics in pediatric patients:

No studies have been performed in pediatric patients.

Gender:

There was no significant difference in the pharmacokinetics of RAVIVO between male and female patients.

Kidney failure:

The clearance and plasma elimination half-life of RAVIVO was significantly reduced in patients with renal insufficiency (creatinine clearance <50 mL / min) and dose adjustment is required to prevent accumulation in these patients. Hemodialysis and continuous ambulatory peritoneal dialysis have no effect on the removal of RAVIVO from the body.

Liver failure:

No studies have been conducted with patients with hepatic impairment. Based on the very limited metabolism of RAVIVO, its pharmacokinetics are thought to be unaffected in liver failure.

5.3. Pre-clinical safety data

Acute toxicity:

The lethal dose 50 (LD50) values were 1500-2000 mg / kg in mice and rats. Reaction to treatment was decreased locomotor activity, increased salivation, ptosis and respiratory depression. At higher doses, death occurred following tremor and convulsions.

The administration of 500 mg / kg orally to monkeys had no effect other than vomiting.

Toxicity at repeated doses:

In rats and monkeys, one-month and six-month studies showed no dose-side effects of 20 mg / kg / day in rats and 62 mg / kg / day in monkeys.

Genotoxicity:

RAVIVO does not cause gene mutation in bacterial or mammalian cells. However, hamster rodents have been shown to cause chromosomal abnormalities in lung cells in vitro without metabolic activation at concentrations of 100 μg / mL and above. It has not been shown in mutagenic toxicity in in vitro tests.

Phototoxic potential

Studies in mice have shown that levofloxacin has only very high doses of phototoxic activity after oral and intravenous administration. Levofloxacin showed no genotoxic potential in photomutagenicity assays and decreased tumor growth in photocarcinogenicity assays.

Carcinogenic potential:

Carcinogenic potential was not demonstrated in 2-year studies on rats at oral doses of 10, 30 and 100 mg / kg / day.

Toxicity to joints:

As with other fluoroquinolones, RAVIVO has been shown to have an effect on articular cartilage (blister and cavity formation) in rats and dogs. These findings were more prominent in young animals.

6. PHARMACEUTICAL PROPERTIES

6.1. List of excipients

Microcrystalline cellulose
Crospovidone
Hydroxypropylmethyl Cellulose
Sodium stearyl fumarate
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc

6.2. Incompatibility

Not valid.

6.3. Shelf-life

Our preparation is in solid dosage form and the shelf life is 36 months in accordance with the preliminary examinations.

6.4. Special precautions about storage

Store at room temperature below 25^{o}C and in a dry place. Protect from light.

6.5. Properties and content of packing

7 film tablets in box, white opaque PVC / PVDC aluminum foil blister package

6.6. Disposal of medicinal products and other special precautions

Unused products or waste materials must be disposed of in accordance with the "Medical Waste Control Regulation" and the ve Packaging and Packaging Waste Control Regulation ".

7. MARKETING AUTHORIZATION HOLDER

Drogsan İlaçları San. ve Tic. A.Ş.
Oğuzlar Mah. 1370. Sok 7/3
6520 Balgat- ANKARA

8. MARKETING AUTHORIZATION NUMBER

216/5

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF AUTHORIZATION

First registration date: 29.05.2008 (In Turkey)

License renewal date:

10. DATE OF REVISION OF THE TEXT

28/05/2019