Turkey

RAVIVO 500 mg/100 ml I.V. Solution for Infusion

PATIENT INFORMATION LEAFLET

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WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITE (inflammation or tearing of the muscles to the bones) AND TENDON RUNNING, PERIPHERAL NEUROPATHY (disorders seen in the nerves away from the center - loss of sensation), CENTRAL NERVOUS SYSTEM AFFECTS, AND MYSTENIA GRAVIS (a kind of muscle weakness disease).

- Fluoroquinolones, including RAVIVO, may cause irreversible adverse reactions leading to disability as follows:
  - Tissue inflammation that connects muscles to bones (tendinite; symptoms can be severe pain in the joints, swelling and redness) and laceration of tissue connecting the muscles to the bones (tendon) (Symptoms are severe pain in the muscles, sudden and rapid bruising, weakness, inability to move)
- Disorders seen in the distant nerves for any reason - loss of sensation (peripheral neuropathy; symptoms, pain in the nerves, tenderness with numbness in the feet and hands, weakness in the muscles, tremors in the hands)
  - The effects of the central nervous system (symptoms may be imagination, anxiety, mental breakdown, suicidal tendency, insomnia, severe headache and confusion)

If any of these undesirable effects occur during the use of RAVIVO, stop using RAVIVO immediately and talk to your doctor or pharmacist.

Fluoroquinolones, including RAVIVO IV, may exacerbate muscle weakness in patients with myasthenia gravis (a kind of muscle weakness disease) If you have a known muscle weakness, talk to your doctor or pharmacist before using RAVIVO.

RAVIVO 500 mg / 100 ml vial containing IV infusion solution

Sterile

It is administered intravenously.

- **Active pharmaceutical ingredient:** In a 100 ml infusion solution, 512 mg levofloxacin hemihydrate equivalent to 500 mg levofloxacin
- **Excipients:** Sodium chloride, sodium hydroxide, hydrochloric acid, water for injection

Please read the LEAFLET carefully before you start using this medication as it involves important information for you.

• Keep this leaflet. You may need to read it again later.

• If you have further questions, please consult your doctor or pharmacist.

• This medication is prescribed specifically for you; please do not give it to others.

• Tell your doctor that you are on this medication when you go to the doctor or hospital while using this medication.

*• Please follow what is written in this leaflet. Do not use **over or below** the dose recommended for you.*

This patient information leaflet includes the following headings:

1. What is RAVIVO and what is it used for?

RAVIVO is a clear, yellow, transparent homogenous solution applied intravenously. Total of 100 ml solution contains 5 mg levofloxacin per 1 ml and a glass bottle and hanger in the container of your medicine.
RAVIVO is an effective antibiotic against bactericides. It belongs to the group of antibiotics called fluoroquinolones. It prevents the growth of the bacteria, their multiplication and it provides the destruction of the bacteria.

RAVIVO is used to treat infections caused by bacteria that are sensitive to levofloxacin, the active substance.
Your doctor may prescribe this RAVIVO form to be administered intravenously because you are unable to take oral antibiotic treatment because you have one of the following conditions:

- Community-acquired pneumonia (pneumonia)
- Complicated kidney and urinary tract infections, including inflammation of the urinary tract and kidney (pyelonephritis)
- Prostate inflammation
- Skin and soft tissue infections: Abse (pus incision), cellulite, furuncles, impetigo (contagious superficial microbial infection of the skin), pyoderma (pus skin infection), uncomplicated skin and skin patch infections caused by wound infections.
- Hospital acquired pneumonia (pneumonia)
- Exposure to airborne anthrax microbes

2. Precautions before the use of RAVIVO

DO NOT USE RAVIVO in the following situations.

If;

- You are allergic to levofloxacin or to any of the components in this medication or to something else from the group of fluoroquinolones antibiotics,

- You have Sara (epilepsy) disease,
- You experienced tendonit disorder (tendonitis) due to the quinolone group antibiotic use (The tendon is a bond that connects the muscle and the skeleton.)
- You are pregnant,
- You are breastfeeding,
- In children and adolescent who continue to grow up

Please do not use RAVIVO.

- It should not be used in children because of the risk of harming the developing cartilage tissue, in adolescents growing up, during pregnancy and in women who breastfeeding.

USE RAVIVO in the following situations CAREFULLY.

If;

Any of the following occurs during use of RAVIVO, stop using RAVIVO immediately and talk to your doctor or pharmacist.

- Tissue inflammation that connects muscles to bones (tendinite; symptoms can be severe pain in the joints, swelling and redness) and laceration of tissue connecting the muscles to the bones (tendon) (Symptoms are severe pain in the muscles, sudden and rapid bruising, weakness, inability to move)
- Disorders seen in the distant nerves for any reason - loss of sensation (peripheral neuropathy; symptoms, pain in the nerves, tenderness with numbness in the feet and hands, weakness in the muscles, tremors in the hands)
    - The effects of the central nervous system (symptoms may be imagination, anxiety, mental breakdown, suicidal tendency, insomnia, severe headache and confusion)
- These reactions can be seen within hours or weeks after starting use of RAVIVO. Patients, in any age group or without pre-existing risk factors, experienced these

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

- If you have had muscle weakness before,
- If you have a very severe lung infection or serious hospital infection (use of another antibiotic may be more appropriate)
- If you have a discomfort related to your central nervous system and you have experienced involuntary contractions,
- If you have brain damage due to stroke or other brain injuries
- In cases of intestinal inflammation with bloody, irregular diarrhea due to prolonged use of antibiotics: If severe, persistent and / or bloody diarrhea occurs during or after treatment of RAVIVO, treatment of RAVIVO should be terminated immediately and appropriate supportive and / or specific treatment should be initiated without delay. Inform your doctor immediately. Your doctor will determine the appropriate treatment for you.
- Risks of tendon rupture increase if pain in the tendons of the muscles that may suggest an inflammation or tear, redness, movement restriction occurs and in the elderly and in patients using corticosteroid. Your doctor may want to monitor this situation closely.
- If you have kidney failure: Your doctor will give you a specific dose adjustment.
- Albeit rarely, it has been reported to develop sensitivity to light in patients that used RAVIVO. Do not expose to strong sunlight or use artificial ultraviolet rays such as solarium during RAVIVO use and for 48 hours after treatment is finished.
- Superinfection (onset of a second infection in the weak individual with any infection): As with other antibiotics, long-term use can result in excessive proliferation of non-resistant organisms. Your doctor may want to follow you closely with the aim of preventing this. If superinfection occurs, it will apply appropriate treatment methods.

If prolongation of QT interval is present in you (a condition that can lead to severe arrhythmias in the heart and sudden deaths): Very rarely, prolongation of QT interval has been reported in patients receiving fluoroquinolone, including levofloxacin. The following risk groups should be cautious.

- If you are advanced age (over 65 years) or female,
- If you have a liver problem,
- If you are using corticosteroids,
- Uncorrected electrolyte imbalance (e.g. low levels of potassium and magnesium in the blood)
- Congenital QT syndrome (a condition that can lead to serious arrhythmias in the heart and sudden deaths)
- Heart disease (heart failure, heart attack history, slowing of heart beat)
- Concomitant use of drugs known to prolong QT interval (e.g. Class IA and III rhythm regulating drugs, some depression drugs, macrolide antibiotics and antipsychotics)

- If you have an innate deficiency of an enzyme called glucose-6-phosphate dehydrogenase,
- Hypoglycemia (decrease in blood sugar level) and hyperglycemia (increase in blood sugar level): If you have diabetes (diabetes) and you are using insulin or oral medications for this, your blood sugar may fall or the resulting coma may develop or your blood sugar may rise (your doctor may ask you to check your blood sugar on a regular basis).
- You have peripheral neuropathy (disorders that occur for any reason in the nerves-loss of sensations)
- Exacerbation of Myastenia Gravis (a kind of muscle weakness disease): Fluoroquinolones have an activity that inhibits muscle-nerve conduction and may exacerbate muscle weakness in patients with myasthenia gravis. In patients with myasthenia gravis using fluoroquinolone respiratory failure that required respiratory

support and post-marketing severe side effects, including death, have been associated with fluoroquinolone. Patients with myasthenia gravis history should avoid fluoroquinolone use.

- Hypersensitivity reactions: Following the first dose, severe hypersensitivity reactions (face and throat swelling as a result of allergies) that have a seldom lethal potential can be seen. You should interrupt your treatment and apply to your doctor for emergency measures.
- Severe diseases in the skin with bubbles filled with water: RAVIVO can cause severe skin reactions such as Stevens-Johnson syndrome (inflammation with blood blister around the skin and eyes, swelling and redness) and toxic epidermal necrolysis (a severe illness with fluid-filled bubbles in the deep). In this case, please apply to your doctor immediately before continuing treatment.
- Very rarely, a single dose of levofloxacin can lead to suicidal thoughts and dangerous behavior. In this case, your doctor may terminate your treatment and determine the appropriate treatment for you.
- If you have a psychological discomfort or a psychiatric illness, use RAVIVO with caution.
- If you have anorexia, jaundice, dark urine, itching or abdominal tenderness during your treatment, contact your doctor immediately. Your doctor may terminate the treatment and determine the appropriate treatment for you.

Please consult your doctor if these warnings apply to you, even at any time in the past.

Use of RAVIVO with food and beverage

- In terms of implementation method, there is no interaction with food and beverages.

Pregnancy

Please consult your doctor or pharmacist before using this medication.

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

The potential risk for humans is unknown. RAVIVO should not be used during pregnancy due to the lack of adequate data on humans and the demonstration of the risk of damaging weight bearing cartilage in growing organisms during experimental studies with fluoroquinolones,

If you notice that you are pregnant during your treatment, please consult your doctor or pharmacist immediately.

Breast-feeding

Consult your doctor or pharmacist before using this medication.

There is insufficient / limited information about levofloxacin being excreted in human or animal milk. It can not be ignored that there is a risk for the breast-feeding child because of physicochemical and direct pharmacodynamic / toxicological data for the excretion of levofloxacin by milk. RAVIVO should not be used during breast-feeding because of the risk of damaging weight bearing cartilage in growing organisms in experimental studies with fluoroquinolones.

Vehicle and machine use

The use of RAVIVO can lead to some undesirable side effects like dizziness,visual disturbances, drowsiness that may impair the patient's ability to concentrate and react. In situations that require special attention, such as vehicle and machine use, the reduction in these abilities may constitute a risk.

If you experience such side effects while using RAVIVO, do not use vehicle and machinery.

Important information about some of the excipients in the content of RAVIVO

If you are not hypersensitive to the excipients contained in the RAVIVO, no adverse effect is expected due to these substances.

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.

Use with other drugs:

- Theophylline, a drug that expands the bronchi and facilitates breathing (when used in conjunction with RAVIVO, the brain contraction threshold falls)
- Similar non-steroidal anti-inflammatory drugs such as fenbufen, ketoprofen, ibuprofen, aspirin, and indomethacin (when used in combination with RAVIVO, brain contraction threshold falls)
- Provenesid used in gout disease or cymetidine used in stomach ulcer (Reduces body excretion of RAVIVO)
- Cyclosporine, a drug that suppresses the immune system (longer half life)
- Vitamin K antagonists used to prevent blood clotting (e.g., warfarin). The effect may increase, the risk of bleeding may occur. Your doctor may ask you for blood clotting tests.
- Medications known to prolong the QT interval in the heart (which can lead to severe arrhythmia in the heart)
  - Class Ia antiarrhythmics (quinidine) and class III antiarrhythmics (amiodarone) (drugs used against heart arrhythmia.)
  - Some depression medications (tricyclic antidepressants, e.g., amitriptyline, impramine)
  - Macrolides (an antibiotic group)
  - Antipsychotics (used in the treatment of some mental illnesses)
- Corticosteroid (used in the treatment of asthma and inflammation)
- A urine test making for opiates which is strong painkillers may give false positive results when using this drug.

Other medicines: Digoxin, glibenclamide and ranitidine are not expected to change the RAVIVO's effect.

Please inform your doctor or pharmacist if you are using or have recently used any medicine with or without a prescription.

How to take RAVIVO?

Instructions for proper use and dose / application frequency:

RAVIVO will be given to you by a specialist healthcare provider, slowly, for at least 60 minutes.

RAVIVO is used in adults.

The dosage depends on the type and severity of the infection as well as on the susceptibility of the bacteria.

Depending on your condition, your doctor may switch to oral administration (RAVIVO 500 mg film tablet) a few days after the initial intravenous administration.

It is recommended that RAVIVO be administered at the following doses:

Type of Infection	**Dose Every 24 hours (according to the severity of infection)**	**The Duration of Treatment**
Community Acquired Pneumonia	Single dose or 2 times 500 mg daily	7-14 days
Inflammation of the urinary tract and kidney (Pyelonephritis)	500 mg	7-10 days
Complicated kidney and Urinary Tract Infection	500 mg	7-14 days
Skin and soft tissue infections	Daily once 250 mg or single dose/twice daily 500 mg	7-14 days
Prostate infection	500 mg	28 days
Hospital acquired pneumonia	750 mg	7-14 days
Airborne anthrax exposure	500 mg	8 weeks

The duration of treatment depends on the course of your disease (see table above). As with all antibiotic treatments in general, the use of RAVIVO should be continued for at least 48-72 hours after the patient has received evidence that the infection has ceased and the fever has dropped.

Administration way and method

RAVIVO should only be administered by slow infusion into a vein by an expert medical personnel. The infusion time should be 60 minutes for 500 mg RAVIVO.

The solution must be visually inspected before use. Only free of particles and clear solutions should be used.

After the rubber stopper has been drilled, the infusion solution must be used immediately to prevent contamination.

Sunlight protection

Do not expose yourself to direct sunlight while using this medicine. Your skin may become more sensitive to the sun and may cause burning, tingling or severe blister. For this reason, use sunscreen with a high protection factor. Wear a hat and clothing that will not leave your arms and legs exposed to the sun. Avoid sunbathing.

Different age groups

Use in children:

RAVIVO is not used in children and adolescents who are growing up.

Use in the elderly:

If there is no abnormality in renal function in the elderly, there is no need to adjust the dose of RAVIVO.

Special use cases:

Kidney failure:

If your kidney function is impaired, your doctor will reduce the dose of RAVIVO and will monitor you more closely.

In patients with creatinine clearance ≤ 50 ml / min, the dosage will be determined by your doctor.

Liver failure:

In liver dysfunction, adjustment in the dose of RAVIVO is not necessary.

Your doctor will tell you how long your treatment of RAVIVO will continue. Do not interrupt your treatment without consulting your doctor.

If you have an impression that the effect of RAVIVO is too strong or weak, consult to your doctor or pharmacist.

If you use more RAVIVO than you should:

If you use RAVIVO than you should, you should speak to a doctor or pharmacist.

The RAVIVO will be administered by a qualified healthcare personnel as often as your doctor considers appropriate.

If you forget to use RAVIVO:

Your doctor will decide when the skipped dose will be administered. Follow the instructions of your doctor for the new administration time of the following dose.

Do not take double doses to compensate for forgotten doses.

Possible side effect after termination of usage RAVIVO:

Do not terminate your RAVIVO treatment without consulting your doctor, the symptoms of your disease may reappear and resistance to bacteria may develop.

4. What are the possible side effects?

As with all medications, side effects may occur in people who are sensitive to the substances found in the content of RAVIVO.

The side-effects in this section are given with an estimation of the frequency;

Very common: It can be seen in at least one of the 10 patients.

Common: It can be seen in less than one in 10 patients, but more than one in 100 patients

Uncommon: It can be seen in less than one in 100 patients, but more than one in 1000 patients.

Rare: It can be seen in less than one in 1000 patients, but more than one in 10.000 patients.

Very rare: It can be seen in less than one in 10.000 patients.

Unknown: It is unpredictable according to the available data.

If any of the following conditions occur, stop using RAVIVO and tell your doctor IMMEDIATELY or contact the emergency department of the hospital nearest to you:

Rare:

- Along with common itching and rashes on the skin, swelling of the lips and face and throat and tongue, difficulty swallowing or breathing (hypersensitivity-anaphylaxis)
- Tendinitis,
- Muscle weakness

Unknown:

- Tendon rupture (inflammation or rupture of the tissues that bind the muscles to the bones)
- Peripheral neuropathy (for any reason disorders seen in the nerves which away from the center- loss sensation)
- Stevens-Johnson syndrome, erythema multiforme (inflammation with blood blister around the skin and eyes, swelling and redness), toxic epidermal necrolysis (a serious disease with deep fluid-filled bubbles on the skin)

These are all very serious side effects.

If you have them, you may need urgent medical attention or hospitalization.

If you notice any of the following conditions, tell your doctor IMMEDIATELY or contact the emergency department of the hospital nearest to you:

Rare:

- Pain and inflammation in your tendons (muscle ligaments). The Achilles tendon is the most frequently affected tendon and in some cases the tendon may break.
- Involuntary seizures of the muscles (convulsions).

Unknown:

- Loss of appetite, the white part of the eye and skin turn the yellow colour ,darkening of the urine, itching, tenderness in the abdominal region. These can be indicative of liver problems that can be sometimes fatal.
- Exacerbation of Myasthenia gravis (a kind of muscle weakness disease)
- Distortion in heart rhythm, palpitation
- Fever, tingling, pain or numbness. These may be signs of neuropathy.
- Severe, persistent, bloody diarrhea combined with severe abdominal pain like cramp and high fever.
- Rupture of joint ligaments and muscles, joint inflammation.
- These may be signs of serious bowel problems.
- All these are serious side effects. Immediate medical attention may be required.

If you notice any of the following situations, tell your doctor:

Common:

- Nausea, vomiting, diarrhea
- Increase in levels of some liver enzymes in blood
- Redness, pain, tenderness in the area where solution is administered intravenously
- Blood vessel inflammation (phlebitis)
- Headache, dizziness

- Insomnia

Uncommon:

- Fungal infections, consist of resistance to other micro-organisms
- Itching and skin eruption, rash, excessive sweating
- Abdominal pain, indigestion, loss of appetite, gas in your stomach, constipation
- Vertigo
- Anxiety, mental confusion, irritability
- Sleepiness, shaking, disorder of taste sensation
- Shortness of breath (dyspnea)
- Joint or muscle pain
- Blood tests may show unexpected results due to liver or kidney problems (bilirubin, increase in creatinine)
- Decrease in the number of white blood cells (leukopenia)
- Fatigue

Rare:

- Decrease in blood sugar. This is important for diabetic patients and may cause coma.
- Visual and auditory hallucinations and excessive skepticism (paranoia) may accompany psychiatric disorders and unrest and depression
- Abnormal dreams, nightmares
- Visual disturbances including blurred vision
- Tinnitus
- Muscle weakness. This is an important condition for myasthenia gravis (a rare disease of the nervous system) patients.
- Low blood pressure
- Acceleration of the heart beat, pulsation

- Bleeding and bruising can easily occur due to decreased count of blood platelet (thrombocytopenia)
- Decrease in the number of white blood cells (neutropenia)
- Fever
- Changes in renal function, kidney failure caused by allergic kidney reactions called interstitial nephritis

Very rare:

- Attacks in patients with porphyria (a methabolic disease that can be seen rarely)

Unknown:

- Coma due to decrease in blood sugar
- Increase in blood sugar
- Self-injurious behavior, including suicidal ideation and suicide attempts
- Loss of taste sensation
- odor disorders including loss of sense of smell
- Fainting (syncope), benign intracranial hypertension (increase benign internal pressure of the head)
- Deterioration of hearing ability, hearing loss
- Temporary visual loss
- Increased skin sensitivity to sun and ultraviolet light (sensitivity to light)
- Decrease in count of all blood cells (pancytopenia) or red blood cells (anemia). The skin may be pale and yellow due to damage to red blood cells and a decrease in the number of all type of blood cells. Fever, sore throat and a general feeling of illness may occur.
- Inflammation in the mouth (stomatitis)
- Excessive immune responses may occur (hypersensitivity).
- Movement and gait problems (dyskinesia, extrapyramidal disorder)

- Breathing difficulty and wheezing (bronchospasm)
- Allergically-induced pneumonia
- Inflammation of blood vessels arising from allergic reaction
- Inflammation of the pancreas (pancreatitis)
- Pain (back, chest, arms and legs)

These are the minor side effects of RAVIVO.

If such symptoms become uncomfortable or continue for a long time, contact your doctor.

If you encounter any side effects not mentioned in these instructions for use inform your doctor or pharmacist.

5.How To Store RAVIVO?

Keep out of the reach and sight of children.

Store at room temperature below 25°C.

After unpacking, the durability in room light is 3 days.

Use in accordance with the expiration date.

Do not use the RAVIVO after the expiration date which is stated on the container.

Do not use the RAVIVO if you notice any defects in the product and / or its packaging.

Do not throw away any expired or unused medicines! Give to the collection system determined by the Ministry of Environment and Urbanization.

Marketing Authorization Holder

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Date of Revision of the Text

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22/04/2019