Module 1.3.1.2 Patient Information Leaflet

Patient Information Leaflet of Multiflex Levoflex 500 mg/100 mL I.V. Solution for Infusion was presented on following pages.

PATIENT INFORMATION LEAFLET

WARNING: SERIOUS SIDE EFFECTS INCLUDING TENDINITIS and TENDON RUPTURE (inflammation or tearing of tissues connecting muscles to bones), PERIPHERAL NEUROPATHY (disorders of the distant nerves for any reason - loss of sensation), central nervous system EFFECTS and exacerbation ofMYASTHENIA GRAVIS (a type of muscle weakness disease)

Antibiotics called fluoroquinolone, including levofloxacin, one of the active ingredients in MULTİFLEX LEVOFLEX, can cause injuries and irreversible undesirable effects such as:

- **Tissue that connects muscles to bones (tendinitis; symptoms may be severe pain in joints, swelling and redness) and tearing of tissue (tendon) connecting muscles to bones, (symptoms may be severe pain in muscles, sudden and rapid bruising, weakness, inability to move)**
- **Disorders seen in distant nerves for any reason- loss of sensation (peripheral neuropathy; symptoms may include pain in the nerves, tenderness, numbness in the feet and hands, numbness in the muscles, weakness in the hands, tremor in the hands).**
- **Central nervous system (central nervous system) effects (symptoms of vision (hallucination), anxiety (anxiety), mental breakdown (depression), suicidal tendencies, insomnia, severe headache and confusion of mind (confusion) can be)**

If you experience any of these undesirable effects during the use of MULTİFLEX LEVOFLEX, stop using MULTİFLEX LEVOFLEX immediately and talk to your doctor or pharmacist.

- **Antibiotics called fluoroquinolone, including levofloxacin, the active ingredient in MULTİFLEX LEVOFLEX, can exacerbate muscle weakness in patients with myasthenia gravis (a type of muscle weakness disease). If you have a known muscle weakness, talk to your doctor or pharmacist before using MULTİFLEX LEVOFLEX.**

MULTİFLEX LEVOFLEX 500 mg / 100 mL I.V. solution for infusion

Sterile

Administered by intravenously.

- ***Active Ingredient:*** Contains 512.48 mg levofloxacin hemihydrate, equivalent to 500 mg levofloxacin in 100 mL infusion solution
- ***Excipients:*** Sodium chloride, hydrochloric acid, sodium hydroxide (for pH adjustment), water for injection

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- *Keep this leaflet. You may need to read it again.*
- *If you have any further questions, ask your doctor or pharmacist.*
- *This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.*
- *Tell your doctor that you are taking this medicine when you go to the doctor or hospital during the use of this medicine.*
- *Follow exactly what is written in this instruction. Do not use high or low doses other than the recommended dosage.*

What is in this leaflet:

1. What MULTİFLEX LEVOFLEX is and what it is used for?

MULTİFLEX LEVOFLEX is a clear, greenish yellow solution applied intravenously.

MULTIFLEX LEVOFLEX is available in 100 ml PP bag with single output with protective Al overpouch, of solution, each containing 5 mg of levofloxacin in 1 ml.

MULTIFLEX LEVOFLEX is an antibiotic effective against bacteria. It is included in the group of antibiotics called fluoroquinolon. It prevents to growth, proliferation of bacteria and eliminates them. MULTIFLEX LEVOFLEX is used in the treatment of infections caused by bacteria that are susceptible to levofloxacin, the active substance of it.

Your doctor may prescribe this intravenous MULTIFLEX LEVOFLEX because you are unable take oral antibiotic treatment for one of the following conditions:

- Community-acquired pneumonia (pneumonia)
- Complicated renal and urinary tract infections including inflammation of the urinary tract and kidney(pyelonepphritis)

- Prostate inflammation
- Complicated skin and soft tissue infections: Uncomplicated skin and skin structure infections caused by wound infection including abscesses, cellulitis, furuncle, impetigo(deep infectious superficial microbial infection), pyoderma(purulent skin infection)
- Hospital-acquired pneumonia
- Exposure to airbone anthrax microbes

2. What you need to know before you use MULTİFLEX LEVOFLEX

DO NOT USE MULTİFLEX LEVOFLEX

If ;

- You are allergic to levofloxacin, any other floroquinolone antibiotics, or any of the other ingredients of this medicine,
- You have ever had epilepsy
- You have ever had a problem with your tendons such as tendonitis that was related to treatment with a 'quinolone antibiotic'. A tendon is the cord that joins your muscle to your skeleton.
- You are pregnant,
- You are breast-feeding,
- You are a child or a growing teenager
- It should not be used in children, in growing adolescents, during pregnancy and in breastfeeding women because of the risk of damage to the developing cartilage tissue.

USE MULTİFLEX LEVOFLEX CAREFULLY if you;

Serious adverse reactions that cause injury and potentially irreversible, including tendinitis (swelling, pain around the joint) and tendon rupture, peripheral neuropathy (pain, numbness, needling and muscle weakness at the ends of the body) and central nervous system effects.

Fluoroquinolones, including MULTİFLEX LEVOFLEX, have been associated with serious side effects that can cause injury and are potentially irreversible. Common side effects include: muscle skeleton and peripheral nervous system (tendon inflammation, tendon rupture, swelling or inflammation of tendons, tingling or numbness, numbness in arms and legs, muscle pain, muscle weakness, joint pain, swelling in joints) atralji (joint pain), myalgia (muscle pain), peripheral neuropathy and central nervous system effects (hallucination, anxiety, depression, suicidal tendencies, insomnia, severe headache and confusion of mind).

These effects can be seen within hours or weeks of starting MULTİFLEX LEVOFLEX. Patients from all age groups or who did not have pre-existing risk factors experienced these sideeffects.

MULTİFLEX LEVOFLEX should be discontinued immediately if initial signs or symptoms of any serious side effects occur. Also, use of fluoroquinolones, including MULTİFLEX

LEVOFLEX, should be avoided in patients who experience any of these serious side effects in connection with fluoroquinolones.

If,

- You have a very severe lung infection or a serious hospital infection (use of another antibiotic may be more appropriate)
- You have a condition that concerns your central nervous system and you have experienced involuntary contractions related to it
- You have brain damage due to stroke or other brain injures
- You suffer from enteritis with bloody, watery diarrhea due to prolonged use of antibiotics: Severe, persistent and/or bloody diarrhea occurs during or after MULTİFLEX LEVOFLEX treatment, MULTİFLEX LEVOFLEX treatment should be terminated immediately and appropriate supportive and/or specific treatment should be initiated without delay. Contact your doctor immediately. Your doctor will prescribe the appropriate treatment for you.
- Risk of tendon rupture increase in elderly and in patients who use corticosteroids and when pain, redness, limitation of movement occurs in the tendons that may suggest inflammation or rupture. Your doctor may want to monitor this situation closely.
- You have renal failure: Your doctor will adjust the dose for you.
- It has been reported that patients who use MULTİFLEX LEVOFLEX rarely develop sensitivity to light. Do not expose to strong sunlight or artificial ultraviolet rays such as solarium during the use of MULTİFLEX LEVOFLEX and for 48 hours after the treatment.
- Superinfection (the beginning of a second infection in the structure weakened by ny infection): As with other antibiotics, long term use can result in excessive proliferation of non-resistant organisms. Your doctor may want to monitor you closely to prevent this condition. Superinfection occurs; appropriate treatment methods will be applied.
- You have prolonged QT interval (a condition that can lead to severe arrhythmias and sudden deaths in the hearth): Very rarely, prolongation of QT interval has been reported in patients using fluoroquinolone, including levofloxacin. Care is required in following risk groups:
    - If you have elderly (over 65 years) or female
    - If you have experienced a liver problem
    - If you have using corticosteroids
    - Uncorrected electrolyte imbalance (e.g. low levels of potassium and magnesium)
    - Congenital QT syndrome (a condition that can lead to serious cardiac arrhythmias and sudden deaths)
    - Hearth disease (hearth failure, history of heart attack, slowing of hearth beat)
    - Co-administration of drugs known prolong the QT interval (e.g. Class IA and III rhythm regulating drugs, some depression drugs, macrolide antibiotics and antipsychotics)

- You have an innate deficiency of an enzyme called glucose-6-phosphate
- Hypoglycemia (decrease in blood sugar level) and hyperglycemia(increase in blood sugar level): If you have diabetes and you are using insulin or oral medication, your blood sugar may decrease or an associated coma may occur or your blood sugar may rise (your doctor may ask you to check your blood sugar regularly).
- You have peripheral neuropathy (disorders that occur for any reason in the nerves- sensory loss).
- Exacerbation of Myasthenia 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. Post-marketing serious side effects, including respiratory failure requiring respiratory support and death have been associated with fluoroquinolone in patients with myasthenia gravis using fluoroquinolone. Patients with a history of myasthenia gravis should avoid fluoroquinolone use.
- Hypersensitivity reactions: Following the first dose, severe hypersensitivity reactions (swelling of the face and throat due to allergy), which are seldom lethal, can be seen. You should stop your treatment and ask your doctor for urgent medical care.
- Severe diseases with blisters on the skin: MULTİFLEX LEVOFLEX can lead to severe skin reactions such as Stevens-Johnson syndrome (inflammation with infiltration swelling and redness on the skin and around the eyes), and toxic epidermal necrolysis (a serious disease with blisters on the skin). In this case, please contact your doctorimmediately before continuing treatment.
- Very rarely, a single dose of levofloxacin can lead to suicidal thoughts and dangerous behavior. In this case, your doctor may stop your treatment and prescribe an appropriate treatment for you.
- If you have a history of psychological or psychiatric disorder, use MULTİFLEX LEVOFLEX with caution
- If you experience loss of appetite, jaundice, dark urine, itching or tenderness during your treatment, contact your doctor immediately. Your doctor may stop your treatment and prescribe an appropriate treatment for you.

If these warnings are valid for you, even in any period in the past, please consult your doctor.

Use of MULTİFLEX LEVOFLEX with food and drink

No interaction with food and drink because of the method of administration.

Pregnancy

Consult your doctor or pharmacist before using this medicine.

No adequate data is available on the use of levofloxacin in pregnant women. The potential risk to humans is unknown. MULTİFLEX LEVOFLEX should not be used during pregnancy due to insufficient data on humans and experimental studies with fluoroquinolones show a risk of damaging weight-bearing cartilage in growing organisms.

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

Breast-feeding

Consult your doctor or pharmacist before using this medicine.

The are no or insufficient information on the excretion of levofloxacin into human or animal milk. The risk for the breastfed child cannot be ruled due to physicochemical and available pharmacodynamics/toxicological data for the excretion of levofloxacin by milk. MULTIFLEX LEVOFLEX should not be used during breastfeeding since experimental data suggest a risk of damage by fluoroquinolones to the weight-bearing cartilage of the growing organism.

Driving and using machines

Use of MULTİFLEX LEVOFLEX may cause some undesirable effects such as dizziness/vertigo, visual disturbances, drowsiness may impair the patient's ability to concentrate and react. Reduced ability may constitute a risk in situations where these abilities are of special importance e.g. driving car or operating machinery.
Patients who experience such side effects when using MULTİFLEX LEVOFLEX should not driving a car or operating machinery.

Important information about some of the excipients in MULTİFLEX LEVOFLEX

If you are not hypersensitive to the excipients contained in MULTİFLEX LEVOFLEX, an adverse effect is not expected.

This medicine contains 15,4 mmol (354 mg) of sodium per 100 mL dose. This should be taken into consideration by patients on a controlled sodium diet.

Other medicines and MULTİFLEX LEVOFLEX

- Theophylline, a drug that facilitates breathing by enlarging the bronchi (when combined with MULTIFLEX LEVOFLEX, the contraction threshold in the brain decreases)

- Non-steroidal anti-inflammatory drugs (NSAIDS) - such as fenbufen, ketoprofen, ibuprofen, aspirin and indomethacin. (You are more likely to have a fit (seizure) if taken with MULTİFLEX LEVOFLEX.)

- Probenecid – used for gout and cimetidine – used for ulcers and heartburn. (Reduces the excretion of MULTİFLEX LEVOFLEX from the body)

- Cyclosporine, a drug that suppresses the immune system (prolongs its half-life)

- Vitamin K antagonists used to prevent blood clotting (e.g. warfarin): The effect may increase risk of bleeding may occur. Your doctor may request blood clotting tests.

- Drugs known to prolong the QT interval in heart (It may cause abnormal heart rhythm):
    - Class IA antiarrhythmic(quinidine) and Class III antiarrhythmic (amiodarone)
    - Some drugs for depression e.g. (tricyclic antidepressants such as amitriptyline and imipramine)
    - Macrolides (an antibiotic group)
    - Antipsychotics (used for psychiatric disorders)
- Corticosteroids (used for inflammation and asthma)

- Urine tests may show ‘false-positive’ results for strong painkillers called ‘opiates’ in people having this drug.

Other drugs: MULTİFLEX LEVOFLEX was not affected when was administered together with the following drugs: digoxin, glibenclamide and ranitidine.

Please inform your doctor or pharmacist if you are currently using any prescription or non-prescription medicine or if you have recently used it.

3. How to use MULTİFLEX LEVOFLEX

MULTİFLEX LEVOFLEX is administered by slow intravenous infusion (infusion lasting at least 60 minutes) by health staff.

MULTİFLEX LEVOFLEX is used in adults.

The dose will depend on the type and severity of infection and also on the sensitivity of the bacterium, which is the causative agent of the infection.

Depending on your condition, it may be possible to change from initial intravenous administration to oral administration (levofloxacin 500 mg tablets) at the same dosage within a few days.

MULTİFLEX LEVOFLEX is recommended the following doses:

Indication	**Daily dose** *(according to severity of infection)*	**Duration of treatment**
Community-acquired pneumonia	500 mg once or twice daily	7 - 14 days
Urinary tract and kidney inflammation (Pyelonephritis)	500 mg once daily	7 - 10 days
Complicated renal and urinary tract infections	500 mg once daily	7-14 days
Skin and soft tissue infections	250 mg once daily or 500 mg one or twice daily	7 - 14 days
Prostate inflammation	500 mg once daily	28 days
Hospital-acquired pneumonia	750 mg once daily	10 - 14 days
Exposure to airbone anthrax microbes	500 mg once daily	8 weeks

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

obtained.

Method of administration

MULTİFLEX LEVOFLEX is administered by slow intravenous infusion by health staff.
The infusion time must be 60 minutes or more for 500 mg MULTİFLEX LEVOFLEX solution.

The solution must be visually inspected before use. Only clear solutions without particles should be used.

100 mL Polypropylene bag, in aluminum over-pouch, closed with twist-off cover. After being removed from the outer packaging (aluminum overpouch), the shelf life is 3 days. Once the twist-off is punctured, it should be used immediately (within 3 hours). This medicinal product is for single use only.

Sunlight protection

Keep out of direct sunlight while having this medicine. Because your skin will become much more sensitive to the sun and may burn, tingle or severely blister. Therefore, use high factor sun cream. Wear a hat and clothes which cover your arms and legs. Avoid sun beds.

Different age groups

Use in children:

MULTİFLEX LEVOFLEX must not be given to children and growing adolescents.

Use in the elderly:

No adjustment of dose is required in the elderly, if there is no impairment of renal function.

Special cases for use:

Renal failure:

If you have impaired renal function, your doctor will reduce the dose of MULTİFLEX LEVOFLEX and monitor you more closely.

For patients with creatinine clearance less than 50 mL / min, the dosage will be determined by your doctor (depending on the severity of the infection)

Hepatic failure

No adjustment of MULTİFLEX LEVOFLEX dose is required in hepatic failure

Your doctor will tell you how long your treatment will take with MULTİFLEX LEVOFLEX. Do not stop your treatment without consulting your doctor.

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

If you use more MULTİFLEX LEVOFLEX than you should have:

Consult to a physician or pharmacist if you have used more MULTİFLEX LEVOFLEX than you

should use.

MULTİFLEX LEVOFLEX will be administered by qualified medical personnel as often as your doctor considers it appropriate.

If you forget to use MULTİFLEX LEVOFLEX

Your doctor will decide when to administer the missed dose. Follow your doctor's instructions for the time of new administration of the following dose.

Do not use a double dose to make up for a forgotten dose.
Possible side effects one MULTİFLEX LEVOFLEX treatment is concluded

Do not stop your MULTİFLEX LEVOFLEX treatment without consulting your doctor, symptoms of your disease may reappear and resistance to bacteria may develop.

4. Possible side effects

Like all medicines, MULTİFLEX LEVOFLEX may have side effects in people who are sensitive to substances in its content.

Other side effects are classified as shown in the following categories:

Very common: Can be seen in at least one of 10 patients.
Common: Less than one in 10 patients, but more than one in 100 patients.
Uncommon: Less than one in 100 patients, but more than one in 1,000 patients.
Rare: Less than one in 1,000 patients, but more than one in 1,000 patients.
Very rare: less than one in 10,000 patients.
Unknown: cannot be estimated from the data available.

If you have any of the following, stop using MULTİFLEX LEVOFLEX and IMMEDIATELY tell your doctor or contact the emergency department of your nearest hospital:

Rare:
You have an allergic reaction. The signs may include: a rash, swallowing or breathing problems, swelling of your lips, face, throat, or tongue.

Unknown:
Stevens-Johnson syndrome, erythema multiforme (blood sitting on the skin and around the eye, inflammation with swelling and redness), toxic epidermal necrolysis (a serious disease in the skin with fluid-filled bubbles)

These are all very serious side effects. If you have one of these, you are severely allergic to MULTIFLEX LEVOFLEX. You may need urgent medical attention or hospitalization.

If you notice any of the following serious side effects, tell your doctor or contact the emergency department of your nearest hospital:

Rare:

- Pain and inflammation in your tendons or ligaments which could lead to rupture. The Achilles tendon is affected most often
- Fits (convulsions)

Unknown:

- Loss of appetite, yellowing of your skin or white of your eyes, dark colored urine, itching or abdominal pain or tenderness. These may be signs of liver problems that may be sometimes fatal.
- Exacerbation of myasthenia gravis (a type of muscle weakness disease)
- Alterations of the hearth rhythm, palpitations
- Fever, tingling, pain or lethargy. These may be symptoms of neuropathy.
- Severe cramp-like abdominal pain and high fever with severe, persistent, bloody diarrhea
- Rupture of joint ligaments and muscles, joint inflammation

These are all serious side effects. You may need urgent medical attention. Serious side effects are very rare.

Common:

- Nausea, vomiting, diarrhea
- Increase in the level of some liver enzymes in your blood
- Redness, pain, tenderness at the site of infusion
- Blood vessel inflammation (phlebitis)
- Headache, feeling dizzy
- Sleeping problems

Uncommon:

- Fungal infections, growth of resistance in other bacteria
- Itching and skin rash, severe itching or hives (urticaria), sweating too much (hyperhidrosis)
- Abdominal pain, indigestion, loss of appetite, feeling bloated (flatulence), constipation
- Dizziness (vertigo)
- Feeling stressed (anxiety), feeling confused, feeling nervous,
- Sleepiness, trembling, changes in the way things taste,
- Shortness of breath (dyspnea)
- Joint pain or muscle pain
- Blood tests may show unusual results due to liver (bilirubin increased) or kidney (creatinine increased) problems
- Decrease in the number of white blood cells (leukopenia)
- Fatigue

Rare:

- Reduced blood sugar. This is important for diabetic patients and may cause to coma.
- Psychiatric disorders that can accompany visual and auditory hallucinations

(hallucinations) and excessive skepticism (paranoia), restlessness, depression

- Abnormal dreams, nightmares
- Visual impairments including blurred vision
- Tinitus
- Muscle weakness. This is an important condition for patient with myasthenia gravis(a rare disorder of the nervous system)
- Low blood pressure
- Increased heartbeat, palpitations
- Decrease in the number of blood platelets (thrombocytopenia) leading to a deficiency to bruise and bleed easily
- Decrease in the number of white blood cells (neutropenia)
- Fever
- Alterations in kidney function and kidney failure which may be due to allergic kidney reactions called interstitial nephritis

Very rare:

- Attacks in patients with porphyria (a very rare metabolic disease)

Unknown:

- Coma associated with reduced blood sugar
- Increased blood sugar
- Self-destructive behavior, including suicidal thoughts and suicide attempts
- Loss of sense of taste
- Impaired sense of smell including loss of sense of smell
- Fainting (syncope), benign intracranial hypertension (benign pressure increase in the head)
- Impaired hearing ability, hearing loss
- Transient visual loss
- Increased skin sensitivity to sun and ultraviolet light (light sensitivity)
- Decrease in number of all blood cells (pancytopenia) or red blood cells (anemia).
- Pale and yellow skin due to the damage in red blood cells and the decrease in the number of all kinds of blood cells. Fever, sore throat and a general feeling of illness may occur
- Inflammation in the mouth (stomatitis)
- Excessive immune responses may develop (hypersensitivity).
- Movement and gait problems (dyskinesia, extrapyramidal disorder)
- Breathing difficulty and wheezing (bronchospasm)
- Allergy-induced pneumonia
- Inflammation of blood vessels caused by allergic reaction

- Inflammation of pancreas(pancreatitis)
- Pain (back, chest, arms and legs)

These are mild side effects of MULTİFLEX LEVOFLEX.

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

If you notice any side effects not mentioned in this patient information leaflet, please inform your doctor or pharmacist.

Reporting of suspected adverse reactions

If you get any side effects not listed in this leaflet, talk to your doctor or pharmacist. You can also report side effects directly to your doctor or pharmacist. You can also report side effects directly to your country's related health authority. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store MULTİFLEX LEVOFLEX

Keep MULTİFLEX LEVOFLEX out of the reach and sight of children.
Keep at room temperature below 25 ° C and original package by protecting from light.

After being removed from the outer packaging (aluminum overpouch), the shelf life is 3 days.

Once the twist-off has been punctured (rubber stopper perforated) the solution should be used immediately (within 3 hours).

Use in accordance with the expiry date.

Do not use this medicine after the expiry date which is stated on the package.

Do not use *MULTİFLEX LEVOFLEX* if you notice that any defects in the product and / or packaging.

Marketing Authorization Holder : HAVER FARMA İlaç A.Ş.
Akbaba Mah. Maraş Cad.
No.:52/2/1 Beykoz / İstanbul

Manufacturing Site: Osel İlaç San. ve Tic. A.Ş.
Akbaba Mah. Maraş Caddesi No:52
Beykoz / İstanbul

This patient information leaflet approved in 07/10/2020