SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: TENDINITIS AND TENDON TIP, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND SERIOUS ADVERSIONS INCLUDING THE VIOLATION OF MYASTENIA GRAVIS

- Fluoroquinolones, including CİPRODEKS, can cause irreversible and irreversible adverse reactions such as:Tendinit ve tendon yırtılması
    - Peripheral neuropathy
    - Central nervous system effects

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

- Fluoroquinolones, including CİPRODEKS, may exacerbate muscle weakness in patients with myasthenia gravis. CİPRODEKS should be avoided in those with a known myasthenia gravis history.

- Since it is known that fluoroquinolone drugs, including CİPRODEKS, are associated with serious adverse reactions, no other alternative can be used in the following indications.
    - Acute bacterial sinusitis
    - Uncomplicated urinary infection

1. NAME OF THE MEDICINAL PRODUCT

CİPRODEKS 2 mg/ml Solution for I.V. Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:

Each mL of infusion solution contains 2.54 mg of ciprofloxacin lactate equivalent to 2 mg of ciprofloxacin. 100 mL solution contains 200 mg ciprofloxacin, 200 mL solution contains 400 mg ciprofloxacin.

Excipients:

Dextrose anhydrous 5,0 g/100 mL

See section 6.1 for excipients.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colorless solution.
The pH value of the infusion solution ranges from 3.5 to 4.6.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It should not be used in acute bacterial sinusitis and uncomplicated urinary infections due to the risk of serious side effects in the presence of alternative treatment options. In addition, sensitivity should be demonstrated with antibiogram in urinary infections.

Adults

- Complicated and uncomplicated infections caused by pathogens sensitive to ciprofloxacin.
- Respiratory infections:

It is indicated for the treatment of pneumonia caused by Klebsiella, Enterobacter spp, Proteus spp, E. coli, Pseudomonas aeruginosa, Haemophilus spp, Moraxella catarrhalis, Legionella spp and Staphylococcus.

It is especially indicated for infections of the middle ear (otitis media) and paranasal sinuses (sinusitis) caused by gram-negative organisms or Staphylococci, including Pseudomonas aeruginosa.

- In eye infections (in bacterial endophthalmit treatment and prophylaxis)
- Kidney and / or urinary tract infections
- In infections of genital organs including prostatitis adnexitis
- In abdominal cavity infections such as gastrointestinal tract, biliary tract infections, peritonitis
- Skin and soft tissue infections
- Bone and joint infections
- In Septicemia
- In infections of patients with weakened immune systems (eg, in patients treated with immunosuppressors or neutropenic) or or prophylactically when there is a high risk of infection
- In selective intestinal decontamination of immunocompromised patients,

Current official guidelines regarding the proper use of antibacterial agents should be observed.

<u>Children</u>

Ciprofloxacin can be used in complicated urinary tract infections and in the 2nd and 3rd line treatment of pyelonephritis in children and adolescents between the ages of 1-17.

The use of ciprofloxacin in pediatric patients with complicated urinary tract infections and pyelonephritis should be limited to infections caused only by ciprofloxacin-sensitive organisms, according to antimicrobial susceptibility data.

Ciprofloxacin can be used in children in the treatment of acute pulmonary exacerbation (age range in clinical trials: 5-17 years) due to P. aeruginosa infection of cystic fibrosis.

Treatment should be initiated after careful risk / benefit assessment due to possible adverse effects on the joints and / or surrounding tissues.

Clinical studies in children are available only for the indications mentioned above.
Sufficient data are not available for other indications.

Anthrax (seen after exposure to Bacillus anthracis) in adults and children:
It is indicated to reduce the occurrence of the disease or slow its progression, following exposure to airborne Bacillus anthracis.

Serum concentrations of ciprofloxacin achieved in humans provide predetermination of clinical benefit and form the basis for the use of ciprofloxacin in inhaled anthrax. (See Section 5.1. - Anthrax Through Breathing - Additional Information)

4.2. Posology and method of administration
Posology/ Administration frequency and duration:
Unless otherwise recommended by the physician, the following doses are recommended.

<table>
<tr><th colspan="3">Indication</th><th>Daily and single dose in adults for CİPRODEKS mg ciprofloxacin</th></tr>
<tr><td colspan="3">Respiratory infections (depending on severity and organism)</td><td>2 x 400 mg – 3 x 400 mg</td></tr>
<tr><td rowspan="2">Urinary system infections</td><td colspan="2">Acute uncomplicated</td><td>2 x 200 mg – 2 x 400 mg</td></tr>
<tr><td colspan="2">Complicated</td><td>2 x 400 mg – 3 x 400 mg</td></tr>
<tr><td colspan="3">Genital infections
Adnexitis, prostatitis, epididymoorchitis</td><td>2 x 400 mg – 3 x 400 mg</td></tr>
<tr><td colspan="3">Diarrhea</td><td>2 x 400 mg</td></tr>
<tr><td colspan="3">Other infections (See Section 4.1)</td><td>2 x 400 mg</td></tr>
<tr><td rowspan="4">Especially severe and life threatening infections,
Especially in the presence of Pseudomonas, Staphylococci and Streptococci.</td><td colspan="2">Recurrent cystic fibrosis infections</td><td>3 x 400 mg</td></tr>
<tr><td colspan="2">Septicemia</td><td>3 x 400 mg</td></tr>
<tr><td colspan="2">Bone and joint infections</td><td>3 x 400 mg</td></tr>
<tr><td colspan="2">Peritonitis</td><td>3 x 400 mg</td></tr>
<tr><td colspan="3">Patients with immunodepression</td><td>2 x 400 mg – 3 x 400 mg</td></tr>
<tr><td colspan="3">Anthrax through breathing (seen after exposure to Bacillus anthracis)</td><td>2 x 400 mg</td></tr>
</table>

The duration of treatment depends on the severity of the disease and its clinical and bacteriological course. Essentially, treatment should be continued for another 3 days after fever has subsided or clinical symptoms have disappeared.

Adults:
- Up to 7 days in kidney, urinary tract and intra-abdominal infections,
- During the entire neutropenic period in patients with weakened defense mechanism (with immunodepression),
- Maximum 2 months in osteomyelitis,
- 7-14 days for other infections.

Treatment should last for at least 10 days due to the risk of late complications in streptococcal infections.

Treatment period for infections of Chlamydia spp. should be at least 10 days.

The total duration of treatment of inhaled anthrax with ciprofloxacin (i.v. or oral) is 60 days. After suspicion of exposure to *Bacillus anthracis* or confirmation of exposure to *B. anthracis*, administration of ciprofloxacin should be started as soon as possible.

Administration method:
CİPRODEKS should be administered intravenously, in 60 minutes by intravenous infusion. Slow infusion into a wide vein minimizes patient discomfort and reduces the risk of venous irritation. Infusion solution can be given directly or mixed with other compatible infusion solutions.

Unless determined to be compatible for other infusion solutions and therapeutic products, they should be administered separately. Events such as crashing, blurring and discoloration are visual signs of incompatibility.

The pH of the solution may be incompatible with all infusion solutions such as penicillins, heparin solution and therapeutic products, which are not physically or chemically stable. Since the pH of the ciprofloxacin solution is in the range of 3.5-4.6, incompatibility arises especially with solutions that are adjusted to alkaline pH. (The pH of the ciprofloxacin solution is in the range of 3.5 - 4.6).
(Only clear solutions can be used.)

Additional information related with special populations:
Adults
Patients with kidney failure
Recommended doses in patients with kidney failure

Creatine clearance ($mL/dk/1,73m^2$)	**Serum creatinine concentration (mg/100 mL)**	**Total daily ciprofloxacin oral dose**

From 30 to 60	1,4'den 1,9'a	Max 800 mg
Under 30	≥ 2	Max 400 mg

Patients with kidney failure in hemodialysis
In patients with creatinine clearance of 30-60 mL / min / 1.73 m^2 (moderate renal failure) or serum creatinine concentration of 1.4 - 1.9 mg / 100 mL, the maximum daily dose of Ciprofloxacin should be 800 mg.

In cases where creatinine clearance is less than 30 ml / min / 1.73 m^2 (severe renal failure) or serum creatinine concentration is equal to or greater than 2 mg / 100 ml, the maximum daily dose of ciprofloxacin should be 400 mg after dialysis days.

Patients with kidney failure who are constantly receiving ambulatory peritoneal dialysis (SAPD)
Addition of ciprofloxacin intravenous infusion solution to the dialysate (intraperitoneal): 50 mg of ciprofloxacin per liter of dialysate and administered 4 times a day every 6 hours.

Liver impairment;
No dose adjustment is required.

Renal/hepatic impairment;
In patients with creatinine clearance of 30-60 mL / min / 1.73 m^2 (moderate renal failure) or serum creatinine concentration of 1.4-1.9 mg / 100 mL, the maximum daily dose of ciprofloxacin should be 800 mg.

In cases where creatinine clearance is less than 30 mL / min / 1.73 m^2 (severe renal failure) or serum creatinine concentration is equal to or greater than 2 mg / 100 mL, the maximum daily dose of ciprofloxacin should be 400 mg on the dialysis days after dialysis.

Children,
Dose studies have not been performed in children with renal and / or hepatic impairment.

Pediatric population:
Recommended daily doses for children and adolescents

Indication	**Daily intravenous dose of Ciprofloxacin (mg / day)**
Cystic fibrosis infections	3 x 10 mg/kg body weight (< 400 mg/dose)
Complicated urinary tract infections and pyelonephritis	3 x 6 mg/kg – 3 x 10 mg/kg body weight (< 400 mg/dose)
Inhalation anthrax (after exposure)	2 x 10 mg/kg body weight (< 400 mg/dose)

Geriatric population:

Patients with advanced age should take doses as low as possible, taking into account the severity of the disease and creatinine clearance.

4.3. Contraindications

• Hypersensitivity to ciprofloxacin or other quinolones or any component of the product (See Section 6.1).
• Ciprofloxacin and tizanidine in combination (see section 4.5).

4.4. Special warnings and precautions for use

Severe infections and / or severe infections due to gram-positive or anaerobic bacteria.

Regarding severe infections, staphylococcal infections and infections involving anaerobic bacteria, CİPRODEKS should be used with a suitable antibacterial agent.

Streptococcus pneumoniae infections

It is not recommended for the treatment of ciprofloxacin pneumococcal infections due to its limited effectiveness against *Streptococcus pneumoniae*.

Genital system infections

Genital system infections can be caused by *Neisseria gonorrhoeae* isolates resistant to fluoroquinolones. It is important to obtain local information about the prevalence of ciprofloxacin resistance and to confirm sensitivity on the basis of laboratory tests in genital system infections that are thought to be due to *Neisseria gonorrhoeae* or known.

Intra-abdominal infections

Limited data are available on the effectiveness of ciprofloxacin in the treatment of postoperative intra-abdominal infections.

Travel diary

In the selection of ciprofloxacin, information on ciprofloxacin resistance in relevant pathogens in the countries visited should be considered.

Bone and joint infections

Ciprofloxacin should be used with other antimicrobial agents, depending on the results of the microbiological documentation.

Cardiac disorders

CİPRODEKS is associated with QT prolongation (see section 4.8).
When used with drugs that can cause Long QT syndrome / Torsades de Pointes, it may increase the risk of developing long QT syndrome or Torsades de Pointes. Therefore, it should not be used with such drugs.

Since women tend to have a longer initial QTc interval than men, they may be more susceptible to drugs that lead to QTc prolongation. Elderly patients may also be more sensitive to drug-related effects on the QT interval.

When CİPRODEKS is used simultaneously with drugs that can cause the QT interval to be extended (eg, class IA or III antiarrhythmias, tricyclic antidepractors, macrolides, antipsychotics) (see section 4.5) or when used in patients with QT prolongation or torsade de pointes risk factors (eg uncorrected electrolyte imbalance such as congenital long QT syndrome, hypokalemia or hypomagnesaemia, and heart disease such as heart failure, myocardial infarction or bradycardia) should be considered.

Children and adolescents

The use of ciprofloxacin in children and adolescents should follow current official guidelines. Treatment of ciprofloxacin should only be initiated by physicians experienced in the treatment of cystic fibrosis and / or severe infections in children and adolescents.

Like other therapeutic products in the same group, ciprofloxacin has been shown to cause arthropathy on the weight-bearing joints of underdeveloped animals. No drug-related cartilage damage or articular damage was observed in the analysis of safety data regarding the use of ciproflocacin in patients younger than 18 years old, mostly with cystic fibrosis. Treatment should only be started after careful risk / benefit assessment due to possible adverse events associated with joints and / or surrounding tissues.

In pediatric patients, no studies have been conducted on the use of ciprofloxacin in indications other than acute pulmonary exacerbation (5-17 years) due to P. aeruginosa infection of the cystic fibrosis, complicated urinary tract infections caused by E. coli and pyelonephritis (1-17 years). Clinical experience is limited for other indications.

Usage in *P. aeruginosa* infection treatment:

Since *P. aeruginosa* easily gains resistance, culture monitoring should be done periodically.

Complicated urinary tract infections and pyelonephritis

Treatment of urinary tract infections with ciprofloxacin should be considered when other treatments cannot be used and should be based on the results of the microbiological documentation. Clinical studies included children aged 1-17 and adolescents.

Other specific severe infections

It can be used in other severe infections, determined according to official guidelines or when careful risk / benefit assessment is made when other treatments cannot be used, or after traditional treatment has failed, and when microbiological documentation justifies the use of ciprofloxacin. The use of ciprofloxacin in specific severe infections other than those mentioned above has not been evaluated in clinical trials and clinical experience is limited.

As a result, caution is recommended when treating patients with these infections.

The risk / benefit assessment suggests that ciprofloxacin is appropriate for pediatric patients for the treatment of respiratory anthrax. For the dose to be applied to pediatric patients in

anthrax through inhalation, see the sections "Posology and method of administration" and "Pharmacodynamic Properties - Anthrax Through Additional Breathing".

Hypersensitivity
In some cases, hypersensitivity and allergic reactions may occur immediately after the first application (see section 4.8). In such cases, the physician should be informed immediately.

Anaphylactic / anaphylactoid reactions can rarely progress to life shock (see section 4.8). This event can be seen in some cases after the first application. In such cases, CİPRODEKS should be discontinued and medical treatment (shock treatment) started.

Gastrointestinal system
When severe and persistent diarrhea is observed during or after treatment, the physician should be consulted as this symptom can hide serious intestinal disease (life-threatening pseudomembranous colitis) and will need immediate treatment (see section 4.8). In such cases, CİPRODEKS should be discontinued and appropriate treatment should be started (oral 4 x 250 mg / day vancomycin). Therapeutic products that inhibit peristaltic movement are contraindicated in this case.

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

When using CİPRODEKS, tendinitis and tendon rupture (predominantly Achilles tendon) can occur, sometimes even bilaterally, within the first 48 hours of treatment.
Even up to several months after discontinuation of CİPRODEKS treatment, tendon ruptures and inflammation may occur. The risk of tendinopathy may increase in elderly patients or in patients treated simultaneously with corticosteroids.

In case of any signs of tendonitis (eg painful swelling, inflammation), a doctor should be consulted and antibiotic therapy should be discontinued. It is important to keep the affected limb at rest and avoid any unsuitable physical exercise (otherwise the risk of tendon rupture may increase). CİPRODEKS should be used with caution in patients with a history of tendon disorders associated with quinolone treatment.

Serious potentially irreversible adverse reactions that cause disability, including tendonitis and tendon rupture, peripheral neuropathy, and central nervous system effects.

Fluoroquinolones, including CİPRODEKS, have been associated with potentially irreversible serious adverse reactions that can cause disability. Common adverse reactions include musculoskeletal and peripheral nervous system (tendinitis, tendon rupture, swelling or inflammation in tendons, tingling or numbness, numbness in arms and legs, muscle pain,

muscle weakness, joint pain, swelling in joints) atralgia, 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 starting CİPRODEKS. Patients of any age group or without pre-existing risk factors experienced these adverse reactions.

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

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

Central nervous system (FAQ)
As with other fluoroquinolones, CİPRODEKS is known to trigger seizures or lower the seizure threshold. CİPRODEKS, in patients with epileptic patients who previously had a central nervous system disorder (eg, convulsion threshold, decrease, previous convulsion history, decrease in cerebral blood flow, change in brain structure or stroke), due to possible central nervous system undesirable effects, but the benefit / risk ratio of treatment It should be used with care. Cases of status epilepticus have been reported (see section 4.8). If seizures occur, CİPRODEKS should be discontinued.

Psychiatric reactions can occur even after the first administration of fluoroquinolones, including CİPRODEKS. In rare cases, depression or psychotic reactions can lead to suicidal idea / thoughts and to self-harming behavior, such as attempting suicide or suicide (see section 4.8). If the patient develops any of these reactions, CİPRODEKS should be discontinued and appropriate measures should be taken.

Cases of sensory or sensorimotor polyneuropathy have been reported in patients receiving fluoroquinolone, including CİPRODEKS, resulting in paresthesia, hypoesthesia, dysesthesia or weakness. Patients treated with CİPRODEKS should be warned to inform their doctor before proceeding with treatment if neuropathy symptoms such as pain, burning, tingling, numbness or weakness develop (see section 4.8).

Skin
Ciprofloxacin has been shown to cause light sensitivity reactions. Therefore, patients receiving CİPRODEKS should not be exposed to direct sunlight or UV light and treatment

should be discontinued when light sensitivity reactions (sunburn-like skin reactions) occur (see section 4.8).

Cytochrome P450

Ciprofloxacin is known as a moderate inhibitor of CYP 450 1A2 enzymes. Caution should be exercised when co-administered with other therapeutic products (eg tizanidine, theophylline, methylxanthines, caffeine, duloxetine, ropinirol, clozapine, olanzapine) using the same enzymatic route. Concomitant use of tizanidine with ciprofloxacin is contraindicated. Drug-specific adverse effects may be observed associated with increased plasma concentrations due to inhibition of metabolic clearance by ciprofloxacin (see section 4.5). Patients taking these medicines together with ciprofloxacin should be closely monitored for signs of overdose clinically. Serum concentrations (eg theophylline) may need to be determined (see also Section 4.5).

Methotrexate

It is not recommended to use ciprofloxacin with methotrexate (see section 4.5).

Resistance

Bacteria that resist ciprofloxacin can be isolated during or after ciprofloxacin treatment, with or without clinically evident super infection. There may be a special selection risk for ciprofloxacin-resistant bacteria during long-term treatments and when treating hospital infections and / or infections caused by the Staphylococcus and Pseudomonas species.

Renal and urinary system

Crystaluria has been reported associated with the use of ciprofloxacin (see section 4.8). Fluid intake should be well regulated in patients receiving ciprofloxacin and excessive alkalinity of urine should be avoided.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening liver failure have been reported with ciprofloxacin. If any signs and symptoms of liver disease (anorexia, jaundice, darkening in the urine, itching or sensitive abdomen) are found, treatment should be discontinued (see section 4.8). Transaminases may have a temporary increase in alkaline phosphatase levels or cholestatic jaundice, especially in patients treated with CİPRODEKS and previously liver damage (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency

Hemolytic reactions with ciprofloxacin have been reported in patients with glucose-6-phosphate dehydrogenase deficiency. Unless the potential benefit is thought to outweigh the potential risk, the use of ciprofloxacin should be avoided in these patients. In this case, the possible hemolysis condition should be monitored.

Reaction at the injection site

Ciprofloxacin i.v. Local injection site reactions have been reported after administration (see section 4.8). These reactions occur more frequently if the infusion time is 30 minutes or less. They can be seen in the form of local skin reactions that quickly improve after completion of the infusion. If the reaction does not repeat or deteriorate, then i.v. the application is not contraindicated.

Interaction with tests
In vitro potency of CİPRODEKS can suppress mycobacterial reproduction and interact with the *Mycobacterium tuberculosis* culture test and cause false negative results in samples from patients using ciprofloxacin.

Epidemiological studies, especially after the use of fluoroquinolone, aortic in the elderly population reports an increased risk of aneurysm and dissection.

Therefore, fluoroquinolones are found in patients with a positive family history of aneurysm disease, patients with previous aortic aneurysm and / or aortic dissection, patients with other risk factors for aortic aneurysm and dissection, or predisposing conditions (eg Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behçet's disease, hypertension, known atherosclerosis) should be used only after careful benefit / risk assessment and other therapeutic options.

In case of sudden abdominal, chest or back pain, patients should be.advised to contact the emergency room immediately.

Dextrose loading for intravenous formulations
This medicinal product contains 5 g dextrose per 100 ml. Caution should be exercised in patients with dextrose intake, such as patients with kidney failure and diabetes mellitus.

Solutions containing dextrose should be administered with caution to patients with known diabetes mellitus or those with subclinical diabetes and carbohydrate intolerance for any reason. Solutions containing dextrose can be contraindicated in people with hypersensitivity to corn or corn products.

4.5. Interaction with other medicinal products and other forms of interaction
Drugs known to prolong the QT interval
CİPRODEKS should be used cautiously in patients taking drugs known to prolong the QT interval, similar to other fluoroquinolones (eg Class IA and III antiarrhythmias, tricyclic antidepressants, macrolides, antipsychotics) (See Section 4.4).

Probenecid
Probenecid prevents renal excretion of ciprofloxacin. Concomitant use with therapeutic products containing probenecid leads to an increase in CİPRODEKS serum concentration.

Tizanidine

In a clinical study in healthy individuals, an increase in serum concentrations of tizanidine was given with ciprofloxacin. (Cmax increase: 7 times, range: 4-21 times; EAA increase: 10 times, range: 6-24 times). Hypotensive and sedative effects increased due to increased serum concentrations (See Section 4.4 - Cytochrome p450). Therapeutic products containing tizanidine should not be administered with CİPRODEKS (See Section 4.3).

Theophylline
Co-administration of therapeutic products containing ciprofloxacin and theophylline can lead to an undesirable increase in serum theophylline level. In this case, undesirable effects of theophylline may occur and rarely these effects can be life or lethal. If two therapeutic products need to be used together, serum theophylline level should be monitored and theophylline dose should be reduced appropriately (See Section 4.4 - Cytochrome P450).

Other xanthine derivatives
Serum concentrations of said xanthine derivatives have been reported to be increased when products containing ciprofloxacin and caffeine or pentoxifylline (oxpentifiline) are used simultaneously.

Methotrexate
Simultaneous administration of ciprofloxacin and methotrexate may inhibit the transport of methotrexate through the renal tubules, leading to an increase in plasma levels of methotrexate. This may increase the risk of toxic reactions associated with methotrexate. Therefore, patients treated with methotrexate should be carefully monitored when CİPRODEKS therapy is indicated simultaneously.

Phenytoin
A change (increase or decrease) in serum phenytoin levels has been observed in patients receiving ciprofloxacin and phenytoin at the same time. To prevent loss of seizure control associated with low phenytoin levels and to prevent undesirable effects of overdose of phenytoin when CİPRODEKS is discontinued in patients using both substances, it is recommended to monitor phenytoin therapy including simultaneous administration of phenytoin serum concentrations during and immediately after administration of CİPRODEKS and phenytoin.

NSAID (Non-steroidal anti-inflammatory drugs)
In animal studies, the combined use of very high doses of quinolones (gyrase inhibitors) and some non-steroidal anti-inflammatory drugs (excluding acetylsalicylic acid) provoked convulsions.

Cyclosporine
When therapeutic products containing ciprofloxacin and cyclosporine were given concomitantly, a temporary increase in serum creatinine level was observed. Therefore, serum creatinine levels of these patients should be checked twice a week.

Vitamin K antagonists
Simultaneous administration of CİPRODEKS with a vitamin K antagonist may increase the anticoagulant effects of these drugs. The risk can vary depending on the underlying infection, the patient's age and general condition, so it is difficult to determine the contribution of ciprofloxacin to the increase of INR (international normalized rate). INR should be monitored frequently when CİPRODEKS is co-administered with a vitamin K antagonist (e.g. warfarin, acenocoumarol, fenprocoumon or fluindion) or immediately after this administration.

Oral antidiabetic agents
Hypoglycaemia has been reported to occur when Ciprodex and oral antidiabetic agents, such as glibenclamide, glimepiride, are administered simultaneously, possibly because they potentiate the effect of the oral antidiabetic agent (see section 4.8).

Duloxetine
Clinical studies have shown that the simultaneous use of duloxetine with potent CYP 450 1A2 isoenzyme inhibitors such as fluvoxamine may lead to an increase in AUC and Cmax of duloxetine. Although there is no clinical data of a possible interaction with ciprofloxacin, similar effects can be expected with concomitant use (see section 4.4 - Cytochrome P450).

Ropinirole
In a clinical study, the simultaneous use of ropinirol, a CYP450 1A2 isozyme inhibitor, and ciprofloxacin, caused a 60% and 84% increase in Cmax and AUC of ropinirol, respectively. In case of concomitant administration with CİPRODEKS, it is recommended to monitor the adverse effects associated with ropinirol and adjust the dose appropriately (See Section 4.4 - Cytochrome P450).

Lidocaine
Simultaneous use of therapeutic products containing lidocaine in healthy volunteers with ciprofloxacin, a CYP450 1A2 isozyme inhibitor, has been shown to reduce intravenous lidocaine clearance by 22%. Although lidocaine treatment is well tolerated, possible reports of ciprofloxacin associated with ciprofloxacin can be reported in case reports.

Clozapine
Following simultaneous administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine increased by 29% and 31%, respectively. Clinical surveillance and appropriate clozapine dose adjustment are recommended during or immediately after concomitant use with CİPRODEKS (See Section 4.4 - Cytochrome P450).

Sildenafil
The Cmax and AUC values of sildenafil increased approximately twice in healthy individuals following a 50 mg oral dose administered concurrently with 500 mg ciprofloxacin. Therefore, when CİPRODEKS is prescribed with sildenafil, risks and benefits should be considered.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: C

Women with childbearing potential / Contraception (contraception)
There are insufficient data on the use of ciprofloxacin in women of childbearing potential. As a precautionary measure, it is recommended to use a suitable method of contraception.

Pregnancy
Data from the use of ciprofloxacin in pregnant women do not show malformation or fetus / newborn toxicity. Animal studies do not show reproductive toxicity. Based on animal studies, it is not recommended to use CİPRODEKS during pregnancy, as the drug cannot be excluded from the non-adult fetal organism as it can cause joint cartilage damage (see section 5.3).

Animal studies, no evidence of teratogenic effect (malformation) is specified (See Section 5.3).

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

Studies on animals are insufficient in terms of effects on pregnancy / and-or / embryonal / fetal development / and-or / birth / and-or / postpartum development (see section 5.3). The potential risk for humans is unknown.

CİPRODEKS should not be used during pregnancy unless necessary.

Lactation
Ciprofloxacin is excreted in breast milk. Due to the possible risk of articular damage, the use of Ciprodex during breastfeeding is not recommended (See Section 5.3).

Reproduction ability / fertility
For studies on animals, see. Section 5.3.

4.7. Effects on ability to drive and use machines
Fluoroquinolones, including ciprofloxacin, may cause a decrease in the patient's ability to drive or drive due to CNS reactions (see section 4.8). This is especially true when taken with alcohol.

4.8. Undesirable effects
Adverse drug reactions based on all clinical studies with ciprofloxacin (oral, parenteral) are listed in terms of CIOMS III categories by frequency (total n = 51621).

The frequencies of adverse reactions (ADR) reported in the use of ciprofloxacin are summarized below. In each frequency group, undesirable effects are presented in descending order of severity.

Adverse reactions are listed below by system-organ class (MedDRA) and frequency. Frequency levels are defined 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 (it cannot be progressed with the data on hand).

Only ADRs identified during post-marketing surveillance and whose frequency could not be estimated are specified under the heading "unknown".

Infections and infestations

Uncommon: Mycotic super infections
Rare: Antibiotic-induced colitis (very rarely, which can result in death)

Blood and lymphatic system diseases

Uncommon: Eosinophilia
Rare: Leukopenia (granulocytopenia), anemia, neutropenia, leukocytosis, thrombocytopenia, thrombocythemia
Very rare: Hemolytic anemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)

Immune system diseases

Rare: Allergic reaction, allergic edema / angioedema
Very rare: Anaphylactic reaction, anaphylactic shock (life-threatening), serum sickness-like reaction

Metabolism and nutritional diseases

Uncommon: Decrease in appetite and food intake
Rare: Hyperglycaemia, hypoglycaemia

Psychiatric diseases

Uncommon: Psychomotor hyperactivity / agitation
Rare: Confusion and orientation disorder, anxiety reactions, abnormal dreams (nightmare), depression (suicidal idea / thoughts and possibility of self-harming behavior such as suicide attempt or suicide), hallucination
Very rare: Psychotic reactions (idea / thoughts of suicide and probability of self-harming behavior, such as attempting suicide or suicide)

Nervous system disorders

Uncommon: Headache, dizziness, sleep disorders, taste disorders
Rare: Paresthesia (peripheral paralysis) and dysesthesia, hypoesthesia, tremor (tremor), seizures (including status epilepticus), vertigo
Very rare: Migraine, coordination disorder, odor disorders, hyperesthesia, intracranial hypertension (pseudotumor cerebri)
Unknown: Peripheral neuropathy and polyneuropathy

Eye diseases

Rare:	Visual disorders
Very rare:	Visual color distortions

Ear and labyrinth disorders

Rare:	Tinnitus, hearing loss
Very rare:	Hearing impairment

Cardiac diseases

Rare:	Tachycardia
Bilinmiyor:	QT prolongation, ventricular arrhythmia, torsades de pointes *.

Vascular diseases

Rare:	Vasodilation, hypotension, syncope
Very rare:	Vasculitis

Respiratory, chest disorders and mediastinal diseases

Rare:	Dyspnea (including conditions related to asthma)

Gastrointestinal diseases

Common:	Nausea, diarrhea
Uncommon:	Vomiting, gastrointestinal and abdominal pain, dyspepsia, flatulence
Very rare:	Pancreatitis

Hepatobiliary diseases

Uncommon:	Increased transaminase levels, increased bilirubin
Rare:	Hepatic insufficiency, jaundice, hepatitis (non-infective)
Very rare:	Liver necrosis (very rarely can progress to life-threatening liver failure)

Skin and subcutaneous tissue disorders

Uncommon:	Rash, itching, urticaria
Rare:	Light sensitivity reactions, swelling
Very rare:	Petechia, erythema multiforme minor, erythema nodosum, Stevens-Johnson syndrome (life-threatening), toxic epidermal necrolysis (life-threatening)
Unknown:	Acute generalized eczematous pustulosis (AGEP)

Musculoskeletal and Connective Tissue Disorders

Uncommon:	Arthralgia (joint pain)
Rare:	Myalgia, arthritis, increased muscle tone and cramping
Very rare:	Muscle weakness, tendinitis, tendon rupture (mostly Achilles tendon), exacerbation of myasthenia gravis

Kidney and urinary tract diseases

Uncommon:	Renal insufficiency
Rare:	Renal impairment, hematuria, crystalluria, tubulointerstitial nephritis

General disorders and diseases related to the application site

Common:	Injection and infusion site reactions
Uncommon:	Nonspecific pain, discomfort, fever
Rare:	Edema, sweating (hyperhidrosis)
Very rare:	Gait disturbance

Research

Uncommon:	Increased alkaline phosphatase level
Rare:	Abnormal prothrombin level, increased amylase
Unknown:	International Normalization Rate (INR) increase (in patients treated with Vitamin K antagonist)

The following undesirable side effects fall into a higher frequency category in the subgroups of patients receiving intravenous or sequential (oral treatment after intravenous therapy).

* These reactions are adverse reactions from post-marketing studies and patients with a risk factor of QT prolongation in general (see section 4.4).

The undesirable effects mentioned below have a higher frequency category in the subgroups of patients undergoing intravenous or sequential (intravenous to oral) treatment.

Common	Vomiting, temporary increase in transaminases, rash
Uncommon	Thrombocytopenia, thrombocythemia, confusion and orientation disorder, hallucination, paraesthesia and dysesthesia, seizures, vertigo, vision disorders, hearing loss, tachycardia, vasodilation, hypotension, transient hepatic insufficiency, jaundice, renal insufficiency, edema
Rare	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing loss, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

< The preferred term MeDRA is used to describe a particular reaction and its synonyms and related conditions. The ADR term representation is based on MeDRA version 14.0 (except 'Mycotic superinfections' and 'Indeterminate pain').>

Pediatric patients

The above-mentioned arthropathy incidence refers to data from studies for adults. Children often have arthropathy (see section 4.4).

4.9. Overdose and treatment

In some cases, reversible renal toxicity has been reported as an acute, overdose symptom.

Symptoms of overdose include dizziness, tremor, headache, fatigue, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic disorder, as well as crystalluria and hematuria. Reversible renal toxicity has been reported.

Apart from emergency measures, it is recommended to monitor kidney function, including urine pH and acidity, if necessary, to prevent crystalluria. The patient should be given plenty of fluids.

Only a small amount (<10%) of ciprofloxacin is eliminated by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PARTICULARS

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Fluoroquinolones
ATC code: J01MA02

Ciprofloxacin is a synthetic broad-spectrum quinolone antibacterial agent.

Mechanism of Action
Ciprofloxacin has an in vitro activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal property of ciprofloxacin includes inhibition of type II topoisomerase (DNA gyrase) and topoisomerase IV enzymes, which are enzymes necessary for bacterial DNA replication, transcription, repair and recombination.

Resistance Mechanism
In vitro ciprofloxacin resistance is commonly due to topoisomerase-IV and DNA gyra targeted mutations through multiple step mutations. Single mutations may result in decreased sensitivity rather than clinical resistance, but multiple mutations often result in cross-resistance between clinical ciprofloxacin resistance and the quinolone class.

Resistance mechanisms that inactivate other antibiotics such as permeability barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by the *Qnr* gene has been reported. Resistance mechanisms that render penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines inactive may not inhibit the antibacterial activity of ciprofloxacin, there is no known cross-resistance between ciprofloxacin and another antimicrobial class. Organisms resistant to these drugs may be sensitive to ciprofloxacin.

The minimal bactericidal concentration (MBK) usually does not exceed the minimal inhibitory concentration (MIC) by more than 2 factors.

In vitro susceptibility to ciprofloxacin

The prevalence of acquired resistance may vary geographically and over time, especially in the treatment of serious infections, local information on the resistance is requested for certain species. If necessary, opinions may be sought from experts when the use of the agent for at least some types of infection is questioned and the local prevalence of resistance increases.

The following bacterial strains and species have been shown to be widely susceptible to ciprofloxacin in vitro:

Aerobic Gram-positive microorganisms;
Bacillus anthracis
Staphylococcus aureus (metisiline-duyarlı)
Staphylococcus saprophyticus
Streptococcus spp.

Aerobic Gram-negative microorganisms

Aeromonas spp.	*Moraxella catarrhalis**
Brucella spp.	*Neisseria meningitidis*
Citrobacter koseri	*Pasteurella spp.*
Francisella tularensis	*Salmonella spp.**
Haemophilus ducrevi	*Shigella spp. **
*Haemophilius influenzae**	*Vibrio spp.*
Legionella spp.	*Yersinia pestis*

* Clinically effective.

Anaerobic microorganisms
Mobiluncus

Other microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

The following microorganisms exhibit varying degrees of sensitivity to ciprofloxacin:
Acinetobacter baumannii, Burkholderia cepacia, Camplybacter spp., Citrobacter freundii, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia spp., Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens, Peptostreptococcus spp., Propionibacterium acnes.

The following microorganisms are considered to be resistant to ciprofloxacin by nature:

Staphylococcus aureus (metisiline -dirençli) ve Stenotrophomonas maltophilia, Actinomyces, Enterococcus faecium, Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealitycum, Anaerobik mikroorganizmalar (Mobiluncus, Peptostrococcus, Propionibacterium acnes dışında)

Breathing anthrax - Additional information
Studies have been conducted in the context of experimental animal infections due to inhalation of *Bacillus anthracis* spores; In these studies, when treatment aimed at reducing the number of spores in the organism covered by the infective dose, antibiotics started immediately after exposure were shown to be effective in avoiding the disease.

Recommended use in humans is primarily based on experimental animal data, with limited data from humans with in vitro sensitivity. In adults, two-month ciprofloxacin treatment administered orally at a dose of 500 mg bid (two doses per day) is considered to be effective in preventing anthrax infection. The treating physician takes into account national and / or international documents on anthrax treatment.

Average serum ciprofloxacin concentrations associated with a statistically significant increase in survival seen in the rheusus monkey model of inhaled anthrax are achieved or exceeded in adults and pediatric patients receiving oral or intravenous ciprofloxacin (see 4.2 "Posology and mode of administration").
A placebo-controlled study was performed in rhesus monkeys exposed to average dose of (5-30 LD50) 11 LD50 (~ 5.5x105) of B. anthracis spores taking by respiratory tract. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax culture used in this study is 0.08 mcg / mL.

The mean serum ciprofloxacin concentrations reached in the estimated Tmax (1 hour after administration) after oral administration to Rhesus monkeys until steady varied between 0.98-1.69 mcg / mL. At the next 12-hour dose, the mean steady-state bottom point concentration varied between 0.12-0.19 mcg / mL.

Anthrax-related death was significantly lower (1/9) for animals that started 24 hours after exposure to *B. anthracis* and received 30 days of oral ciprofloxacin treatment compared to the placebo group (9/10) (p = 0.001). Following the 30-day drug administration period, an animal treated with ciprofloxacin died from anthrax.

5.2. Pharmacokinetic properties
General features
The pharmacokinetics of ciprofloxacin has been evaluated in different populations in humans. In adults receiving 500 mg of ciprofloxacin orally every 12 hours, the mean peak serum concentration reached at steady state is 2.97 mcg / mL; The average peak serum concentration reached at steady state after administration of 400 mg ciprofloxacin intravenously every 12 hours is 4.56 mcg / mL. The average valley serum concentration at steady state for both regimens is 0.2 mcg / mL.

In a study of 10 pediatric patients aged 6-16 years, the peak plasma concentration attained after 2 hours of intravenous infusion of 10 mg / kg at 12-hour intervals was 8.3 mcg / mL and valley concentrations varies between 0.09-0.26 mcg / mL. After the second intravenous infusion, patients who undergo oral treatment of 15 mg / kg administered every 12 hours reach an average peak concentration of 3.6 mcg / mL after the first oral dose. Long-term safety data, including the effects of ciprofloxacin on pediatric patients - effects on cartilage - are limited (see section 4.4 for additional information).

Absorbation:
The maximum serum concentration is reached at the end of the infusion after intravenous infusion. Pharmacokinetics intravenously are linear up to 400 mg dose.

Average serum concentrations of ciprofloxacin within the time (hour) after starting infusion. (mg/L)

Time (hour)	100 mg/L iv (30 min. inf.)	200 mg/L iv (30 min. inf.)	400 mg/L iv (60 min.inf.)
0,5	1,8	3,4	3,2
0,75	0,8	1,4	3,5
1	0,5	1	3,9
1,5	0,4	0,7	1,8
2,5	0,3	0,5	1,2
4,5	0,2	0,3	0,7
8,5	0,1	0,1	0,4
12,5	0,04	0,1	0,2

Ciprofloxacin and its metabolites did not accumulate in comparison of dose regimens twice a day and three times a day in terms of pharmacokinetic parameters.

200 mg ciprofloxacin 60 minutes I.V. infusion or 250 mg ciprofloxacin were given orally every 12 hours, and the area under the serum concentration-time profile curve (AUC) was equivalent.

When 400 mg ciprofloxacin was given 60 minutes I.V. infusion or 500 mg ciprofloxacin orally every 12 hours, it was bioequivalent in terms of area under the concentration-time curve (AUC).

The C max value found by 60 minutes I.V. infusion of 400 mg ciprofloxacin is similar to the C max value of the 750 mg oral dose.

400 mg ciprofloxacin every 8 hours is bioequivalent to the area under the concentration-time curve (AUC) of 750 mg oral ciprofloxacin every 12 hours with 60 minutes I.V. infusion.

Distribution:

Ciprofloxacin binds proteins at a low rate (20-30%) and is largely non-ionized in plasma. It diffuses into the extravascular space. In the steady state, the volume of distribution is large (2-3 L / kg) and passes into the tissues at a concentration exceeding the serum level.

Metabolism:
It has been reported to have 4 low concentration metabolites. These metabolites are decethylenepiprofloxacin (M1), sulfosiprofloxacin (M2), oxosiprofloxacin (M3) and formylsiprofloxacin (M4); The in vitro antimicrobial activity of M1 and M3 is comparable to nalidixic acid. The in vitro antimicrobial activity of M4, which is found in a smaller amount, is equivalent to norfloxacin.

Elimination:
Ciprofloxacin is largely excreted unchanged by the renal route. To a smaller extent, it is excluded from the renal pathway, especially faeces.

Excretion of ciprofloxacin (% of dose) Intravenous

	Urine	**Feches**
Ciprofloxacin	61,5	15,2
Metabolites (M1-M4)	9,5	2,6

Renal clearance is 0.18-0.3 L / hour / kg, total body clearance is 0.48-0.60 L / hour / kg. Ciprofloxacin is subjected to glomerular filtration and tubular secretion.

Non-renal secretion of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolism. 1% of the dose is excreted through bile and ciprofloxacin is present in bile in a high concentration.

Characteristic features in patients
Children
In a study conducted in children, Cmax and AUC were not age-dependent. There was no significant increase in Cmax and AUC values following multiple doses (10 mg / kg / 3x1). 10 children with severe septicemia, the C max value was 6.1 mg / L (range 4.6-8.3 mg / L) following 1 hour infusion at the dose level of 10 mg / kg in those younger than 1 year; In children between 1 and 5 years old, C max 7.2 mg / L (range 4.7-11.8 mg / L) was found. AUC values in the respective age groups are 17.4 mg * hour / L (range 11.8-32, 0 mg * hour / L) and 16.5 mg * hour / L (range 11.0-23.8 mg * hour, respectively) / L). These values are within the range reported in therapeutic doses for adults. Based on population pharmacokinetic analysis of pediatric patients with various diseases, the estimated average half-life in children is 4-5 hours, and the bioavailability of oral suspension is about 60%.

5.3. Pre-clinic reliability data
Non-clinical data revealed no specific risks for humans on the basis of conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or reproductive toxicity.

As with a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Photomutagenicity / photocarcinogenicity data showed the weak photomutagenic or phototurogenic effect of ciprofloxacin in in vitro and animal experiments. This effect is comparable to that of other gyrase inhibitors.

Artiküler tolerabilite:
Diğer giraz inhibitörleri için bildirildiği gibi, siprofloksasin olgunlaşmamış hayvanlarda yüksek ağırlık kaldıran büyük eklemlerde hasara neden olur. Kıkırdak hasarının derecesi yaş, tür ve doza göre değişiklik gösterir; bu hasar eklemler üzerindeki ağırlığı alarak azaltılabilir. Olgun hayvanlarla (sıçan, köpek) yapılan çalışmalar kıkırdak lezyonlarına ait kanıt ortaya çıkarmamıştır. In a study with young beagle dogs, ciprofloxacin caused severe articular changes in therapeutic doses after two weeks of treatment, and these changes can still be observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Dextrose Anhydr
Lactic acid
Hydrochloric acid (for pH adjustment)
Injectable water

6.2. Incompatibilities

CİPRODEKS 2 mg / ml Solution for I.V. Infusion is compatible with saline solution, Ringer's solution, Ringer's lactate solution, 10% glucose solution, 10% fructose solution, 5% glucose solution containing 0.45% NaCl. When mixed with the specified infusion solutions, it should be applied within a short time after mixing with respect to microbiological and light sensitivity. Unless proven to be compatible with other infusion solutions and therapeutic products, the infusion solution must be administered separately.

Visual signs of incompatibility are collapse, cloudiness and discoloration. Incompatibility may be observed in combination with all infusion solutions / therapeutic products (eg penicillins, heparin solutions), which are not physically or chemically stable at the pH of the solution (ciprofloxacin infusion solutions containing 5% Dextrose 3.5-4 it is 6).

6.3 Shelf-life

24 months.

6.4. Special precautions for storage

Store at room temperatures below 25°C and protected from light. Do not freeze.

6.5. Nature and contents of the container

CİPRODEKS 2 mg / ml Solution for I.V. Infusion; It is offered in 100 and 200 ml PP bags. It has 2 forms with and without set.

6.6. Demolition of the materials remained from human medical products and other special precautions

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

Preparing for use

CİPRODEKS should be applied with infusion over a period of 60 minutes.

Slow infusion into a wide vein minimizes patient discomfort and reduces the risk of venous irritation.

The infusion solution can be given by mixing with other infusion solutions that it is direct or compatible with.

Cold precipitation may occur and re-dissolve at room temperature; For this reason, it is recommended that the infused solution is not stored in the refrigerator.

7. MARKETING AUTHORISATION HOLDER

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