SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: TENDINITIS AND TENDON DETACHMENT, PERIPHERAL NEUROPATHY, SERIOUS SIDE EFFECTS INCLUDING CENTRAL NERVOUS SYSTEM EFFECTS AND MYASTHENIA GRAVIS

- Fluoroquinolons including VONECİP may cause irreversible adverse effects such as following which may cause disability:
  - Tendinitis and tendon detachment
  - Peripheral neuropathy
  - Central nervous system effects

Use of VONECİP should be immediately terminated in patients who experience any of these reactions and also the use of fluoroquinolon products should be avoided.

- Fluoroquinolons including VONECİP may exacerbate muscular weakness in patients who have myasthenia gravis. Use of VONECİP should be avoided in patient with known history of myasthenia gravis.
- As it is known that drugs belonging to fluoroquinolon group including VONECİP relate to serious adverse reactions, they may be used for below indications if there is not any other alternative.
  - Acute bacterial sinusitis
  - Uncomplicated urinary infection
  - Acute bacterial exacerbation of chronic bronchitis

1. NAME OF MEDICINAL PRODUCT

VONECİP 400 mg/200 ml Solution for I.V. Infusion

Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: 200 ml infusion solution contains 508.0 mg Ciprofloxacin lactate equivalent to 400 mg Ciprofloxacin.

Excipients: Sodium chloride 1800 mg (30.8 mmol)

See Part 6.1 for other excipients.

Electrolyte concentrations (per liter):
Sodium: 154 mmol = 154 mEq
Chloride: 154 mmol = 154 mEq
Lactate: 7.2 mmol = 7.2 mEq

3. PHARMACEUTICAL FORM

Infusion solution.

Clear, almost colourless and slightly yellowish solution.
pH value of infusion solution is between 3.5 and 4.6.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

It should not be used in the condition that acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis and uncomplicated urinary infections, where there are alternative treatments, because of the risk of serious adverse effects.
It can only be used for these indications if it is proved by antibiogram with the approval of infection disease specialist in case the other alternative treatments are not applied.

Adults
• Complicated and uncomplicated infections induced by pathogens sensitive to ciprofloxacin
• Respiratory tract infections:
It is indicated in treatment of pneumonia induced by *Klebsiella, Enterobacter spp, Proteus spp, E. coli, Pseudomonas aeruginosa, Haemophilus spp, Moraxella catarrhalis, Legionella* and *Staphylococcus*.
It is especially indicated in middle ear infections (otitis media) and paranasal sinus infections (sinusitis) induced by gram negative organism including *Pseudomonas aeruginosa* or *staphylococcus.*
• Eye infections (Treatment and prophylaxis of bacterial endophthalmitis)
• Kidney and/or urinary tract infections
• Infections of genital organs including adnexitis, prostatitis
• Infections such as peritonitis, gastrointestinal tract, biliary tract infections
• Skin and soft tissue infections
• Bone and joint infections
• Septicemia
• Infections in patients with weakened immune system (for example, neutropenic patients or treated with immunosuppressive) or as prophylactic where there is a high risk of infection
• Selective intestinal decontamination of patients with suppressed immune system

Updated official directives related to suitable uses of antibacterial agents should be taken into consideration.

Children
Ciprofloxacin may be used in complicated urinary tract system infections and in 2^{nd} and 3^{rd} step treatment of pyelonephritis in children and adolescents between 1-17 years-old.
Use of ciprofloxacin in pediatric patients with complicated urinary tract infections and pyelonephritis should be restricted with infections induced by organisms susceptible to only ciprofloxacin as to antimicrobial susceptibility data.

Ciprofloxacin may be used in treatment of acute pulmonary exacerbations depending on *P.aeruginosa* infection of cystic fibrosis in children. (Age range in clinic studies: 5-17 years-old).
Treatment should be commenced after a careful risk/benefit evaluation due to potential adverse effects related to joints and/or surrounding tissues.
Clinical trials in children are available for only the above-mentioned indications. Sufficient data is not available for other indications.

Inhalation anthrax in adults and children (seen after being exposed to *Bacillus anthracis)*:
It is indicated for reducing emergence of disease and alleviating its progress following being exposed to *Bacillus anthracis* dispersed into air.

Ciprofloxacin serum concentrations achieved in human provides pre-determination of clinic benefit and constitutes the foundation of use of ciprofloxacin in inhalation anthrax. (See: 5.1 Pharmacodynamic Properties Part- Inhalation Anthrax - Additional Information)

4.2. Posology and method of administration

Posology/Frequency and duration of administration:
Unless otherwise prescribed by a physician, the following doses are recommended.

Indication		VONECİP daily and single dose mg ciprofloxacin in adults for
Respiratory tract infections (As to severity and organism itself)		2 x 400 mg – 3 x 400 mg
Urinary tract infections	Uncomplicated	2 x 200 mg – 2 x 400 mg
	Complicated	2 x 400 mg – 3 x 400 mg
Genital infections Adnexitis, prostatitis, epididymoorchitis		2 x 400 mg – 3 x 400 mg
Diarrhea		2 x 400 mg
Other infections (see 4.1 Therapeutic indications)		2 x 400 mg
Especially severe and life-threatening infections, Especially in the presence of *Pseudomonas*, *Staphilococcus* *Streptococcus.*	Infections recurring in cystic fibrosis	3 x 400 mg
	Septicemia	3 x 400 mg
	Bone and joint infections	3 x 400 mg
	Peritonitis	3 x 400 mg
Patients with immunodepression		2 x 400 mg – 3 x 400 mg
Inhalation anthrax (seen after being exposed to		2 x 400 mg

Bacillus anthracis)	

Treatment time depends on severity of disease, clinical and bacteriological course. Essentially, treatment should be continued 3 days more after fever drops or clinical symptoms disappear.
Adults:

- Up to 7 days in kidney, urinary and intra-abdominal infections
- During all neutropenic period in patients with weak deference (immunodepression)
- Maximum 2 months with osteomyelitis
- 7-14 days for other infections

Treatment should be maintained minimum 10 days due to late complication risk in streptococcal infections.

Treatment time should be minimum 10 days in chlamydia infections.

Total treatment time of inhalation anthrax with ciprofloxacin (i.v. or oral) is 60 days. After suspecting to be exposed to *Bacillus anthracis* and confirmed to be exposed to *B. anthracis,* of ciprofloxacin should be administered as soon as possible.

Method of administration:
VONECİP should be administered within a period of 60 minutes with i.v. infusion. Slow infusion to a large vein minimizes disease of patient and reduces risk of venous irritation. Infusion solution may be directly given or by being mixed with other compatible infusion solutions.

Unless it is specified as compatible for other infusion solutions and therapeutic products, it should be administered separately. Incidents such as sedimentation, blurring and color change are visual symptoms of incompatibility.

Incompatibility may arise with penicillin which are not physically or chemically stable in pH of solution, all infusion solutions such as heparin solution and therapeutic products. Since pH of ciprofloxacin solution is within 3.5-4.6 range, incompatibility arises to solutions whose especially alkali is adjusted to pH (between 3.5-4.6 pH ranges of VONECİP).
Only clear solutions can be used.

Special populations:
Adults
Patients with kidney failure
Doses recommended in patients with kidney failure

Creatinin clearance [mL/min/1.73 m^2]	Serum creatinine [mg/100 ml]	Total daily ciprofloxacin oral dose
from 30 to 60	from 1.4 to 1.9	Maximum 800 mg
below 30	≥ 2.0	Maximum 400 mg

Patients with kidney failure in haemodialysis
Maximum daily ciprofloxacin intravenous dose should be 800 mg in patients with creatinin clearance 30-60 ml/min/1.73 m^2 (middle kidney failure) or serum creatinin concentration 1.4-1.9/100 ml.
In cases where creatinin clearance is less than 30 ml/min/1.73 m^2 (severe kidney failure) or serum creatinin concentration is equal to 2.0 mg/100 ml or higher, maximum daily ciprofloxacin intravenous dose should be 400 mg in dialysis days following dialysis.

Patients with kidney failure receiving continuous ambulatory peritoneal dialysis (CAPD)
Addition of ciprofloxacin intravenous infusion solution to dialysate (intraperitoneal): 50 mg ciprofloxacin for each litter of dialysate and applied 4 times a day in 6 hours.

Patients with kidney failure
Dose adjustment is not necessary.

Patients with kidney and liver failure
Maximum daily ciprofloxacin intravenous dose should be 800 mg in patients with creatinine clearance 30-60 ml/min/1.73 m^2 (middle kidney failure) or serum creatinine concentration 1.4-1.9/100 ml.

In cases where creatinine clearance is less than 30 ml/min/1.73 m^2 (severe kidney failure) or serum creatinine concentration is equal to 2.0 mg/100 ml or higher, maximum daily ciprofloxacin intravenous dose should be 400 mg.

Children
Dose study has not been conducted in children with renal and/or hepatic failure.

Paediatric population:
Daily doses recommended for adults and adolescents

Indication	**Daily intravenous ciprofloxacin dose (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)
Inhalational anthrax (post exposure)	2 x 10 mg/kg body weight (< 400 mg/dose)

Geriatric population:
Doses should be taken as low as possible by considering severity of disease and creatinine clearance in elderly patients.

4.3. Contraindications

- In case of hypersensitivity against active agent ciprofloxacin or other quinolone derivative chemotherapeutics or other component of product (See: 6.1 “List of excipients”).
- Co-administration of ciprofloxacin and tizanidin (See 4.5 "Interactions with other medicinal products and other forms of interaction").

4.4. Special warnings and precautions for use

Severe and potentially irreversible adverse reactions that lead to disability including tendonitis and tendon rupture, peripheral neuropathy and central nervous system effects.

Fluoroquinolons including VONECİP is related to serious and potentially irreversible adverse reactions which may cause disability. Common adverse reactions include musculoskeletal and peripheral nervous system (tendinitis, tendon rupture, swelling or inflammation of the tendons, tingling or numbness, numbness in the arms and legs, muscle pain, muscle weakness, joint pain, swelling in the joints), atrialgia, myalgia, peripheral neuropathy and central nervous system effects (hallucinations, anxiety, depression, suicidality, insomnia, severe headache and confusion) (see section 4.8. Undesirable Effects). These reactions may be observed within a few hours or weeks after VONECİP usage. Patients in any age or not having pre-existing risk factors were experienced these adverse reactions. VONECİP must be terminated immediately in case any signs or symptoms of any serious adverse reaction occur. In addition, the use of fluoroquinolones including VONECİP should be avoided in patients who experienced any of these serious adverse reactions in connection with fluoroquinolones before.

Severe infections and/or severe infections depending on gram positive or anaerobic bacteria:
VONECİP should be used an appropriate antibacterial agent in relation to infections where severe infections, staphylococcus infections and anaerobic bacteria are in question.

Streptococcus pneumoniae infections
VONECİP is not recommended in treatment of pneumococcal infections depending on insufficiency of effectiveness against *Streptococcus pneumoniae*.

Genital tract infections
Genital tract infections may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. It is of utmost importance to acquire local information regarding resistance prevalence to ciprofloxacin in genital tract infections known or contemplated to be dependent on *Neisseria gonorrhoeae* and to verify sensitivity in the basis of laboratory tests.

Intra-abdominal infections
There is limited data related to effectiveness of ciprofloxacin in treatment of postoperative intra-abdominal infections.
Travel diarrhea
Information related to ciprofloxacin resistance should be taken into account in relevant pathogens in the visited countries in selection of ciprofloxacin.

Bone and joint infections
Ciprofloxacin should be used together with other antimicrobial agents depending on results of microbiological documentation.

Cardiac disorders
VONECİP is associated with cases of QT prolongation (See: 4.8 Undesirable Effects).

It may increase risk of long QT syndrome or Torsades de Pointes formation when used in combination with drugs causing long QT syndrome/Torsades de Pointese. Thus, it should not be used in combination with such drugs.

Since women have tendency of having longer beginning QTc range when compared with men, they may be more sensitive against drugs causing QTc prolongation. Elderly patients may be more responsive to effects related to drug over QT interval.

When VONECİP is simultaneously used with drugs causing prolongation of QT range (e.g. Class IA or III antiarrhythmic, tricyclic antidepressants, antipsychotics, macrolides) (see: 4.5 interaction with other medicinal products and other interaction forms) or QT prolongation when used in patients bearing torsade de pointes risk factors (for example, Congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesemia and heart diseases such as heart failure, myocardial infarction or bradycardia), it should be careful with the foregoing.

Children and adolescents
Use of ciprofloxacin in children and adolescents should follow existing official guidelines.
Treatment of ciprofloxacin should be initiated by experienced physicians in treatment of cystic fibrosis and/or heavy infections in only children and adolescents.

It has been demonstrated that ciprofloxacin causes arthropathy over joints of undeveloped animals bearing weights such as other therapeutic products in the same group. Drug related articular or cartilage damage has not been witnessed in analysis of reliability data relating to use of ciprofloxacin in patients younger than 18 years old, majority of them have cystic fibrosis. Treatment should be initiated following careful risk/benefit evaluation due to potential adverse incidents in connection with joints and/or surrounding tissues.

A particular study has not been conducted in indications except for complicated urinary tract infections and pyelonephritis (1-17 years) arising from acute pulmonary exacerbation (5-17 years) of cystic fibrosis depending on *P. aeruginosa* infections in pediatric patients. Clinical experience is limited for other indications.

Use in treatment of *P. aeruginosa* infection:
Since *P. aeruginosa* easily acquires resistance, periodic culture follow-up should be conducted.

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

Other specific severe infections
Other severe infections may be utilized when other treatment cannot be used or determined according to official guidelines and after careful risk/benefit evaluation is performed or traditional treatment has become unsuccessful and it poses a justification for use of ciprofloxacin of microbiological documentation. Use of ciprofloxacin in specific severe infections apart from the ones above has not been evaluated in clinic studies and clinic experience is limited. As a result, while treating of patients with these infections, it is recommended to be careful.

Risk/benefit assessment shows that it is suitable to administer ciprofloxacin to pediatric patients for inhalation anthrax. For the dose to be administered to pediatric patients in inhalation anthrax, see "Posology and method of administration" and "Pharmacodynamic Properties-Inhalation Anthrax-Additional Information".

Hypersensitivity
Hypersensitivity and allergic reactions can occur immediately following first administration in some cases (See: “4.8 Undesirable Effects”). In these cases, physician should be immediately informed.

Anaphylactic/anaphylactoid reactions may very rarely progress up to vital shock (See: “4.8 Undesirable effects”). This case can be seen following first administration in some cases. In such cases, VONECİP should be discontinued and medical treatment (shock treatment) should be instituted.

Gastrointestinal tract
Once severe and persistent diarrhea is seen during treatment or thereafter, since this symptom may conceal severe intestinal disease (vital pseudomembranous colitis resulted with death) and it should be treated with immediate effect, physician should be sought (See: “4.8 Undesirable Effects”). In such cases, VONECİP should be discontinued and suitable treatment should be instituted (oral 4 x 250 mg/day vancomycin). Therapeutic products inhibiting peristaltic action are contraindicated in this case.

Musculoskeletal system
VONECİP should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.
While using VONECİP, tendonitis and tendon rupture (mainly Achilles tendon) may arise as both sides even within first 48 hours of treatment. Tendon ruptures and inflammation may occur even up to a few months following discontinuation of VONECİP treatment.

Tendinopathy may be increased in elderly patients and patients treated with corticosteroids at the same time.

At any sign of tendinitis (e.g. painful swelling, inflammation), should be consulted a doctor and ciprofloxacin treatment should be discontinued. It is high importance to keep affected extremity under rest and to avoid inappropriate physical exercise (otherwise, risk of tendon rupture may increase). VONECİP should be used with caution in patients having story of relevant tendon disorder with quinolone treatment.
Exacerbation of Myasthenia Gravis:
Fluoroquinolons have neuromuscular blockage activity and they may aggravate muscle weakness in patients with myasthenia gravis. Severe adverse incidents such as ventilatory support requirement and post marketing including death have been associated with fluoroquinolons in patients with myasthenia gravis using fluoroquinolone. Patients having myasthenia gravis in their stories should avoid using fluoroquinolone.

Central nervous system (CNS)
As in other fluoroquinolone, it is known that VONECİP trigger seizures or seizure threshold. VONECİP should only be used by observing benefit/risk rate of treatment due to side effects of potential central nervous system in patients with central nervous system disorders in epileptic patients (e.g. low convulsion threshold, anamnesis convulsion reduced cerebral blood flow, structural change in brain, stroke). Status Epilepticus cases have been reported (See: "4.8 Undesirable Effects"). In case of seizure, VONECİP should be discontinued.

Including also VONECİP, psychiatric reactions may occur even after first administration of fluoroquinolons. In rare cases, this may include depression or psychotic reactions, suicidal thoughts and attempted suicide or the idea of suicide/self-harm behaviours (See: "4.8 Undesirable Effects"). In case of development of any of such reactions by patient, VONECİP should be discontinued and appropriate measures should be adopted.

Including also VONECİP, sensory or sensorimotor polyneuropathy cases resulted with paresthesia, dysesthesia, hypoesthesia or weakness in patients receiving fluoroquinolons. In the event patients treated with VONECİP develop neuropathy symptoms such as pain, burning, tingling, numbness or weakness, patients should be warned in the issue of informing their physicians before continuing treatment. (See: "4.8 Undesirable Effects").

Skin
It has been shown that ciprofloxacin causes light sensitivity reactions. Thus, patients receiving VONECİP should not be exposed directly to day light or UV light and treatment should be discontinued when light sensitivity reaction occur (skin reactions similar to sunburn) (See: "4.8 Undesirable Effects").

Cytochrome P450
Ciprofloxacin is known as a moderate inhibitor of CYP 450 1A2 enzymes. Care should be given when it is administered together with other therapeutic products (for example,

theophylline, caffeine, methylxanthine, caffeine, duloxetine, clozapine, ropinirole). Co-administration of tizanidin with ciprofloxacin is contraindicated. Drug-specific side effects may be seen in relation with increment plasma concentrations depending on inhibition of metabolic clearances by ciprofloxacin (See also: 4.5 "Interaction with other medicinal products and other forms of interaction"). Patients having taken these drugs together with ciprofloxacin should be closely monitored against clinical overdose symptoms. Serum concentrations (e.g. theophylline) may need to be identified (see also: "4.5 Interaction with other medicinal products and other forms of interaction).

Methotrexate

Ciprofloxacin is not recommended for use in combination with methotrexate (see the section "4.5 interaction with other medicinal products and other forms of interaction").

Resistance

Bacteria resisting ciprofloxacin may be isolated without super infection or in combination with clinical apparent super infection during treatment of ciprofloxacin after treatment period. There may be a special selection risk in terms of bacterial resistant to ciprofloxacin while treating infections induced by hospital infections and/or *Staphylococcus* and *Pseudomonas* species and during long term treatments.

Renal and urinary tract

Relevant crystalluria has been reported related to use of ciprofloxacin (See "4.8 Undesirable effects"). Liquid reception in patients taking ciprofloxacin should be regulated well and excessive alkali of urine should be avoided.

Hepatobilier system

Hepatic necrosis and life threatening hepatic failure incidents have been reported (See "4.8 Undesirable effects"). Treatment should be discontinued in case of symptom and finding of liver disease (anorexia, jaundice, darkening in blood, rash or sensitive abdomen). Specifically, patients treated with VONECİP and having liver damage earlier may have transient increase in alkaline phosphatase or cholestatic jaundice (See: “4.8 Undesirable Effects”).

Glucose-6-phosphate dehydrogenase deficiency

Hemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Unless potential benefit outweighs potential risk, use of ciprofloxacin should be avoided in these patients. In this case, hemolysis case likely to occur with possibility should be monitored.

Reaction in injection site

Local injection site reactions have been reported following i.v. administration of VONECİP (See: “4.8 Undesirable Effects”). If infusion duration is 30 minutes or less, these reactions are more common. They are seen as local skin reactions rapidly corrected following completion of infusion. If reaction does not recur or worsen, thereafter, i.v. administration is not contraindicated.

Interaction with tests
In vitro potency of VONECİP suppresses microbacterial reproduction and may interact with *Mycobacterium tuberculosis* culture test and it may cause incorrect adverse results in samples obtained from patients using ciprofloxacin.

Sodium (0.9% NaCl) loading for VONECİP
With regard to those patients for whom sodium intake is a medical problem (the patients with congestive heart failure, renal failure, nephrotic syndrome etc.), attention must be paid for additional sodium loading.
This medicinal product contains 30.8 mmol of sodium per vial. This should be taken into consideration for patients who are under controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction
Drugs known to prolong QT range
VONECİP should be given carefully when it is used in combination with drugs known to prolong QT range as for fluoroquinolons (e.g. Class IA and III antiaritmics, tricyclic antidepressants, macrolids, antipsychotics) (See: "4.4 Special warnings and precautions for use").

Probenecide
Probenecide inhibits renal excretion of ciprofloxacin. Use of it with therapeutic products containing probenecide leads to rise of serum concentration of VONECİP.

Tizanidin
In a clinical study conducted with healthy subjects, a rise has been seen when administered together with ciprofloxacin in tizanidin serum concentrations. (C_{max} increase: 7 times, range: 4-21 times; AUC increase: 10 times, range: 6-24 times). Hypotensive and sedative effects have increased depending on increased serum concentrations (See: "4.4 Special warnings and precautions for use- Cytochrome P450"). Therapeutic products containing tizanidin should not be administered in combination with VONECİP (See: 4.3 "Contraindications").

Theophylline
Administration of therapeutic products containing ciprofloxacin and theophylline may lead to an undesired increase in serum theophylline level. In this case, side effects pertinent to theophylline may occur and these effects may be rarely vital or lethal. If you need to use two therapeutic products together, serum theophylline level should be monitored and dose of theophylline should be reduced accordingly (see: 4.4 "Special warnings and and precautions for use- Cytochrome P450").

Other Xanthine derivatives
When products containing ciprofloxacin and caffeine or pentoxifylline (oxenpenthyphylline) are simultaneously used, serum concentrations of the said xanthine derivatives have been reported to increase.

Methotrexate
Administration of VONECİP with methotrexate at the same time inhibits transport of renal tubules of methotrexate and may lead to increase in plasma levels of methotrexate. This may increase risk of toxic reactions in connection with methotrexate. Therefore, it is not recommended to use methotrexate in combination with VONECİP (See also 4.4. Special warnings and precautions for use).

Phenytoin
Change has been observed (increase or decrease) in serum phenytoin levels of patients taking VONECİP and phenytoin. It is recommended to monitor phenytoin treatment including measurements of phenytoin serum concentration during simultaneous administration of phenytoin and just after its administration with VONECİP in order for preventing Undesirable effects related to over phenytoin dose when VONECİP is discontinued in patients using both substances and avoiding loss of seizure control related to low phenytoin levels.
NSAIDs (Non-steroidal anti-inflammatory drugs)
Combined use of quinolons (gyrase inhibitors) and some non-steroid anti-inflammatory drugs (except for acetylsalicylic acid) in very high doses in animal studies is seen to trigger convulsions.

Cyclosporine
When ciprofloxacin and therapeutic products containing ciprofloxacin simultaneously are administered, a temporary rise has been observed in serum creatinin level. Thus, serum creatinin levels of these patients should be checked twice a week.

Vitamin K antagonists
Simultaneous administration of VONECİP with one vitamin K antagonist may increase anti-coagulant effects of these drugs. The said risk may vary according to underlying infection, age and general status of patient and thus, it is hard to determine contribution of ciprofloxacin to increase of INR (international normalized ratio). INR should be frequently monitored during administration of ciprofloxacin in combination with one vitamin K antagonist (for example, warfarin, acenocoumarol, phenprocoumon or fluindion).

Oral antidiabetic agents
When oral antidiabetic agents are administered at the same time as primarily sulphonilureas with VONECİP, it has been reported that hypoglycaemia has occurred due to reinforcement of effect of oral antidiabetic agent (See "4.8 Undesirable effects).

Duloxetin
Clinical studies have shown that simultaneous use of duloxetin with strong CYP 450 1A2 isozyme inhibitors such as fluvoxamine leads to increase in AUC and C_{max} values of duloxetin. Though there is no clinical data pertinent to potential interaction with ciprofloxacin, similar effects may be expected in simultaneous use (See: 4.4 "Special warnings and precautions for use-cytochrome P450").

Ropinirole
In a clinical study, simultaneous use of ropinirole that is a moderate CYP450 1A2 isozyme inhibitor with ciprofloxacin has lead to an increase in the rate of 60% and 84% respectively in C_{max} and AUC values of ropinirole. In case of simultaneous administration with VONECİP, it is recommended to monitor side effects related to ropinirol and to appropriately adjust dose (See: 4.4 "Special warnings and precautions for use- Cytochrome P450").

Lidocaine
It has been shown that simultaneous use of therapeutic products containing lidocaine with ciprofloxacin that is CYP450 1A2 isozyme inhibitor in healthy volunteers has reduced intravenous lidocaine clearance in the rate of 22%. Though lidocaine treatment is well tolerated, potential side effects related to ciprofloxacin likely to occur in simultaneous administration are reported in case reports.

Clozapine
Following simultaneous administration of 250 mg ciprofloxacin with clozapine for a period of 7 days, clozapine and N-desmethylclozapin serum concentrations have respectively increased in the rate of 29% and 31%. Clinic surveillance and appropriate clozapine dose adjustment are recommended during simultaneous use with VONECİP or just after that (See: 4.4 "Special warnings and precautions for use- Cytochrome P450").

Sildenafil
Sildenafilin C_{max} and AUC values have increased nearly two folds following 50 mg oral dose simultaneously administered with 500 mg ciprofloxacin in healthy subjects. Consequently, in case VONECİP is prescribed in combination with sildenafil, risk and benefits should be taken into consideration.

4.6. Fertility, pregnancy and lactation
General recommendations
Pregnancy category: C

Women of childbearing potential/Contraception
Sufficient data related to use of ciprofloxacin in women having childbearing potential is not available. As a precaution, it is recommended to use a suitable method of contraception.

Pregnancy
Data obtained from use of ciprofloxacin in pregnant women show no malformation or fetal/neonatal toxicity. Animal studies do not show reproductive toxicity. Since the fact that drug causes joint cartilage damage in fetal organism based on animal studies cannot be kept out of possibility (See 5.3 "Preclinical reliability data"), it is not recommended to use VONECİP during pregnancy.

Lactation
Ciprofloxacin is eliminated to breast milk. Depending on the risk potential articular damage VONECİP should not be used during breastfeeding (See: 5.3 "Pre-clinical safety data).

Fertility
See for studies on animals: 5.3 "Pre-clinical safety data".

4.7. Effects on ability to drive and use machines
Fluoroquinolons including ciprofloxacin may cause reduction in car or vehicle use of patient depending on CNS reactions (See: 4.8 “Undesirable effects”). This is especially the case when taken together with alcohol.

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

ADR frequencies reported in use of ciprofloxacin are outlined below. Undesirable effects are provided according to reduced severity order in each frequency group. Adverse reactions are listed according to system-organ class (MedDRA) and frequency degree. Frequency degrees 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 (cannot be estimated by available data).

ADRs defined during only post-market surveillance and whose frequency is not predicted are stated under the title of "unknown".

Infections and infestations
Uncommon: Mycotic super infections
Rare: Antibiotic-induced colitis (which can very rarely resulted with 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 disorders
Rare: Allergic reaction, allergic edema/angioedema
Very rare: Anaphylactic reaction, anaphylactic shock (life-threatening), serum sickness-like reaction

Metabolism and nutrition disorders

Uncommon: Anorexia

Rare: Hyperglycemia, hypoglycemia

Psychiatric disorders

Uncommon: Psychomotor hyperactivity/agitation

Rare: Confusion and disorientation, anxiety reactions, abnormal dreams (nightmare), depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide), hallucinations

Very rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Nervous system disorders

Uncommon: Headache, dizziness, sleep disturbances, taste disorders

Rare: Paresthesias (peripheral paralgesia) and dysesthesia, hypoesthesia, tremor (shaking), seizures (including status epilepticus), vertigo

Very rare: Migraine, coordination disorders, smell disorders, hypoesthesia, and intracranial hypertension

Unknown: Peripheral neuropathy and polyneuropathy

Eye disorders

Rare: Visual disorder

Very rare: Visual color disorders

Ear and labyrinth disorders

Rare: Tinnitus, hearing loss,

Very rare: Decreased hearing

Cardiac disorders

Rare: Tachycardia

Unknown: QT prolongation, ventricular arrhythmia, Torsades de pointes*.

Vascular disorders

Rare: Vasodilatation, hypotension, syncope

Very rare: Vasculitis

Respiratory, thoracic and mediastinal disorders

Rare: Dyspnea (including situations with asthma)

Gastrointestinal diseases

Common: Nausea, diarrhea,

Uncommon: Vomiting, gastrointestinal and abdominal pain, dyspepsia, gas bulge

Very rare: Pancreatitis

Hepatobiliary disorders

Uncommon: Increase in 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, non-specific vesicles
Very rare: Petechiae, erythema multiforme, Erythema nodosum, Stevens-Johnson Syndrome (life threatening), toxic epidermal Necrolysis (life threatening)
Unknown: Acute generalised exanthematous pustulosis

Musculoskeletal and connective tissue disorders

Uncommon: Arthralgia (joint pain), musculoskeletal pain (e.g. extremity pain, back pain, chest pain)
Rare: Myalgia, arthritis, increased muscle tone and cramping
Very rare: Muscle weakness, tendonitis, tendon rupture (mostly Achilles tendon), exacerbation of symptoms of myasthenia gravis

Renal and urinary disorders

Uncommon: Acute renal failure
Rare: Renal disorder, hematuria, crystalluria, tubulo-interstitial nephritis

General disorders and administration site conditions

Common: Infection and infusion site reactions
Uncommon: Non-specific pain, discomfort, fever
Rare: Edema, sweating (Hyperhidrosis)
Very rare: Gait disorder

Investigations

Uncommon: Alkaline phosphatase level increase
Rare: Abnormal prothrombin levels, increased amylase
Unknown: International normalised ratio increased (in patients treated with Vitamin K antagonists

* These reactions are adverse reactions acquired from patients with generally QT prolongation risk factor and from post-market studies. (See: 4.4 "Special warnings and measures for use")
The following undesirable side effects have higher frequency category in patient sub groups to which treatment is applied either intravenously or sequentially. (intravenous and oral)

Common	Temporary increase in transaminases, vomiting, rash
Uncommon	Thrombocytopenia, thrombocythemia, confusion and disorientation, hallucinations, paresthesia and dysesthesia, hypoesthesia, seizures, vertigo, vision disorders, hearing loss, tachycardia, vasodilation, hypotension,

	temporary hepatic failure, jaundice, renal failure, edema
Rare	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraines, decreased hearing, olfactory disorders, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

<MedDra preferred term has been used for clarifying a particular reaction and its synonym and relevant conditions. Term ADR is based on MedDRA version 14.0. (except for 'Mycotic super infections' and 'Vague pain').>

Pediatric patients

Incidence of the above-mentioned arthropathy refers to data obtained from the studies conducted for adults. Arthropathy frequently occurs in children. (See: 4.4 "Special warnings and measures for use")

4.9. Overdose

In some cases acute, reversible renal toxicity have been reported as a symptom of overdose.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.

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

5. PHARMACOLOGICAL PARTICULARS

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02

Ciprofloxacin is a broad-spectrum quinolone antibacterial synthetic agent.

Effect mechanism

Ciprofloxacin has *in vitro* effectiveness against a wide range of gram negative and gram positive microorganisms. Ciprofloxacin bactericide property contains inhibition of type II topoisomerase enzymes (topoisomerase IV and DNA gyrase) that are enzymes necessary for bacterial DNA replication, recombination, repair and transcription.

Resistance Mechanism

In vitro ciprofloxacin resistance mostly depends on mutations targeting DNA gyrase and bacterial topoisomerase through multi-step mutations. Single mutations can result in very

clinical resistance susceptibility; however, multiple mutations may be resulted with cross resistance generally between clinical ciprofloxacin resistance and quinolone class.

Resistance mechanisms inactivating other antibiotics such as permeability barriers (common in *Pseudomonas aeruginosa*) efflux mechanism may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance coded by *Qnr* gene has been reported. Resistance mechanisms inactivating penicillins, cephalosporins, aminoglycosides, macrolides and tetracycline may not inhibit antibacterial effectiveness of ciprofloxacin; there is not a known cross resistance between ciprofloxacin and other anti-microbial class. Organism resistant to these drugs may be susceptible to ciprofloxacin.

Minimal bactericide concentration (MBC) and minimal inhibitor concentration (MIC) are not usually in question more than 2 factors.

In vitro susceptibility to ciprofloxacin
Prevalence of resistance acquired may vary in time and geographically; local information pertinent to resistance for particular species is required in treatment of severe infections. If necessary, in case use of agent is investigated for at least some infection types and local prevalence of resistance increases, opinion should be sought from specialists.

It has been shown that the following listed bacteria types and species are commonly susceptible to ciprofloxacin under *in vitro* conditions.

Aerobic gram-positive Microorganisms
Bacillus anthracis
Staphylococcus aureus (susceptible to methicillin)
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*

* Effectiveness has been clinically demonstrated.

Anaerobic Microorganisms
Mobiluncus

Other Microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae

Mycoplasma hominis
Mycoplasma pneumoniae

The following microorganisms exhibit susceptibility in variable degrees 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, Streptococcus pneumoniae, Peptostreptococcus spp., Propionibacterium acnes.

The below-mentioned microorganisms are accepted to be resistant to ciprofloxacin because of their nature:
Staphylococcus aureus (methicillin-susceptible) and *Stenotrophomonas maltophilia, Actinomyces, Enterococcus faecium, Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealitycum, Anaerobic microorganisms (*except for *Mobiluncus, Peptostrococcus, Propionibacterium acnes*)

Inhalation anthrax-Additional information
Studies within the context of experimental animal infections depending on inhalation of *Bacillus anthracis'* spores have been conducted; when treatment is applied in regard to reducing number of spores in organism within the scope of infective dose, it has been shown that antibiotics started just after exposure are effective in avoiding diseases.

Recommended use in humans has been based on experimental animal data together with restricted data obtained from humans with primarily *in vitro* susceptibility. It is accepted that ciprofloxacin treatment of two months orally administered in 500 mg bid (two doses per day) doses in adults is effective in avoiding anthrax infection. Physician administering treatment takes into consideration national and/or international documents related to anthrax treatment.

Average serum ciprofloxacin concentrations with statistically significant increase of survival seen in rhesus monkey of inhalation anthrax can be reached in adults and pediatric patients to whom oral or intravenous ciprofloxacin is administered or such concentrations are exceeded (See: "4.2 Posology and method of administration").

Placebo-controlled study has been conducted in rhesus monkeys exposed to (5-30 LD_{50}), 11 LD_{50} (~ $5.5x10^5$) inhaled average dose of *B. anthracis'* spores. Minimal inhibitor concentration of ciprofloxacin for anthrax culture used in this study (MIC) is 0.08 mcg/ml.

Average serum ciprofloxacin concentrations attained in T_{max} (after 1 hour from administration) estimated following oral administration conducted until stability state to rhesus monkeys varies between 0.98-1.69 mcg/ml. In next 12 hours dose, attained average stable state deep point concentration varies between 0.12-0.19 mcg/ml.

Death because of anthrax for animals started 24 hours after being exposed to *B. anthracis* and treated with oral ciprofloxacin on daily basis for 30 days has been found as lower significantly (1/9) when compared with placebo group (9/10) (p=0,001). An animal subject to treatment of ciprofloxacin following 30 days drug administration period has died of anthrax.

5.2. Pharmacokinetic properties

General properties

Pharmacokinetics of ciprofloxacin have been evaluated in variable populations in humans. Average peak serum concentration attained in stable state in adults taking 500 mg ciprofloxacin orally in each 12 hours is 2.97 mcg/ml; average peak serum concentration attained in stable state following administration of intravenous 400 mg ciprofloxacin in each 12 hours is 4.56 mcg/ml. Average valley serum concentration in stable state for each two regimes is 0.2 mcg/ml.

Peak plasma concentrations attained following 2 intravenous infusion for 30 minutes in 10 mg/kg dose conducted with 12 hours intervals in a study conducted in 10 pediatric patients between 6-16 years is 8.3 mcg/ml; valley concentrations vary between 0.09-0.26 mcg/ml. Following second intravenous infusion, patients subjected to oral treatment of 15 mg/kg administered once 12 hours attain average peak concentration of 3.6 mcg/ml after first oral dose. Long term reliability data including -effects over cartilage- following administration of ciprofloxacin on pediatric patients is limited (For additional information, see "Special warnings and precautions for use ").

Absorption:

Following intravenous infusion, maximum serum concentration is reached at the end of infusion. Intravenous pharmacokinetic is linear up to 400 mg dose.

Ciprofloxacin average serum concentrations within the time (hour) following commencing infusion administration (mg/l)

Period (hour)	100 mg/l iv (30 minutes. inf.)	200 mg/l iv (30 minutes. inf.)	400 mg/l iv minutes.infusion.)
0.5	1.8	3.4	3.2
0.75	0.80	1.40	3.50
1.00	0.50	1.00	3.90
1.50	0.40	0.70	1.80
2.50	0.30	0.50	1.20
4.50	0.20	0.30	0.70

8.50	0.10	0.10	0.40
12.50	0.04	0.10	0.20

In comparison of intravenous twice and three times dose regimes in terms of pharmacokinetic parameters, it has been seen that ciprofloxacin and metabolites did not accumulate.

200 mg ciprofloxacin has been administered 60 minutes i.v. infusion or 250 mg ciprofloxacin is administered in each 12 hours orally; the area below serum concentration-time profile curve (AUC) are found as equivalent.

400 mg ciprofloxacin has been administered 60 minutes i.v. infusion or 500 mg ciprofloxacin is administered in each 12 hours orally; the area below serum concentration-time profile curve (AUC) are found as bio-equivalent.
C_{max} value of 400 mg ciprofloxacin found with 60 minutes i.v. infusion resembles to C_{max} value of 750 mg oral dose.

The area below concentration-time curve of 400 mg ciprofloxacin in each 8 hours and 750 mg oral ciprofloxacin in each 12 hours with 60 minutes i.v. infusion is bio-equivalent.

Distribution:
Ciprofloxacin binds proteins in low rates (20-30 %) and is found in non-ionized form in great extent in plasma. It diffuses into extravascular clearance. Its distribution volume is large in stable condition (2-3 L/kg) and it penetrates into tissues in concentration exceeding serum level.

Biotransformation:
It has been reported that it has 4 metabolites with low concentration. These metabolites are desethylenciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and phormilciprofloxacin (M4); *in vitro* antimicrobial activity of M1 and M3 is in comparable nature with nalidixic acid. *In vitro* antimicrobial activity of M4 in fewer amounts is equivalent with norfloxacine.

Elimination:
Ciprofloxacin is largely removed in unchange state via renal way Smaller proportion of it is eliminated with especially faeces rather than renal way.

Ciprofloxacin excretion (Dose rate %)

	Intravenous	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites M1-M4	9.5	2.6

Renal clearance is 0.18-0.3 L/hr/kg and total body clearance 0.48-0.60 L/hr/kg. Ciprofloxacin is exposed to glomerular filtration and tubular secretion.
Non-renal secretion of ciprofloxacin depends on active transintestinal secretion up to primary metabolism. 1% of dose is excreted via bile and ciprofloxacin is found in high concentration in bile.

Characteristic properties in patients

Children

C_{max} and AUC have not been found as age-dependent in a study conducted in children. No significant increase has been observed following multiple dose administration (10 mg/kg/3x1) in C_{max} and AUC values. It has been found out that C_{max} value is 6.1 mg/L (range 4.6-8.3 mg/L) following 1 hour infusion in 10 mg/kg dose level in those younger than 1 year out of 10 children having severe septicemia and C_{max} is 7.2 mg/L (range 4.7-11.8 mg/L) in children between 1-5 years. AUC values in relevant age groups are respectively 17.4 mg*hour/L (range11.8-32.0 mg*hour/L) and 16.5 mg*hour/L (range 11.0-23.8 mg*hour/L). These values are within the range reported in therapeutic doses for adults. Population pharmacokinetic analyses of pediatric patients with various diseases are taken as a basis, estimated average half-life in children is 4-5 hours and oral suspension bio-availability is nearly 60%.

5.3. Pre-clinical safety data

Non-clinical data has not revealed any special risk for humans on the basis of traditional studies regarding to single-dose toxicity, repeat-dose toxicity and carcinogenic potential or reproductive toxicity. As in some set of quinolon, ciprofloxacin is phototoxic in animals in exposure levels in respect to clinically related conditions. Photomutagenicity/photocarcinogenicity data has revealed weak photomutagenic or phototumourigenic effect of ciprofloxacin in vitro and animal tests. This effect is in comparable level with effect of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage in large joints lifting heavy weights in immature animals. The degree of cartilage varies according to age, type and dose; this damage can be reduced as weight over joints. Studies conducted with mature animals (rat, dog) have not revealed any proof regarding cartilage lesions. In a study conducted with young beagle dogs, ciprofloxacin has caused severe articular changes in therapeutic doses following two weeks treatment and such change can be even observed after 5 months.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Lactic acid
Hydrochloric acid
Water for Injection

6.2. Incompatibilities
VONECİP infusion solution containing 0.9% NaCl is compatible with serum physiological, Ringer solution, Ringer lactate solution, 5% and 10 % glucose solution, 10% fructose solution, 5% glucose solution containing 0.225% or 0.45% NaCl. When compared with specified infusion solutions, it should be administered within a short time after being compared in terms of microbiological aspect and light sensitivity. Unless it is specified as compatible for other infusion solutions and therapeutic products, it should be administered separately at all times.

Visual signs of incompatibility are collapse, clouding and color change. Incompatibility may be seen in combination with solutions adjusted to especially alkali pH value and all infusion solutions/therapeutic products (for example, penicillins, heparin solutions) not physically and chemically stable in pH value of solution (pH value of VONECİP infusion solution containing 0.9% NaCl is 3.5-4.6)

6.3. Shelf life
24 months.

6.4. Special precautions for storage
Store at room temperature below 30°C.
Do not freeze. Keep out of the light.

For easier use, plug of infusion bottle should go inside the ring located in the centre.
If outer ring penetrates in, stopper of the vial may be damaged.

6.5. Nature and contents of container
Type II glass vial close with a bromobutyl rubber stopper and a flip-off cap, placed in a box.

6.6. Special precautions for disposal
There is no special requirement for its disposal.

Preparation for use:
VONECİP should be administered within a period of 60 minutes with i.v. infusion.

Slow infusion to a large vein minimizes discomfort of patient and reduces risk of venous irritation.

Infusion solution can be directly administered or administered by being mixed with other compatible infusion solutions.
Collapse may occur in cold and may dissolve again in room temperature; for this reason, it is recommended not to store infusion solution in refrigerator.

Unused product or waste materials should be disposed of in compliance with the local regulations.

7. MARKETING AUTHORISATION HOLDER
POLİFARMA İLAÇ SAN. VE TİC. A.Ş.
Vakıflar OSB Mahallesi, Sanayi Caddesi, No:22/1
Ergene/Tekirdağ/TURKEY

8. MARKETING AUTHORISATION NUMBER
2014/640

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of First Authorisation: 28.08.2014

Renewal of the Authorisation: 03.12.2019

10. DATE OF REVISION OF THE TEXT

16.04.2019