SUMMARY OF PRODUCT CHARACTERISTICS

WARNING: TENDINITIS AND TENDON TEAR, PERIPHERAL NEUROPATHY CENTRAL NERVOUS SYSTEM EFFECTS AND SERIOUS SIDE EFFECTS INCLUDING VIOLENCE OF MYASTENIA GRAVIS

- Fluoroquinolones, including CİPROPOL, have been associated with potentially irreversible serious adverse reactions that can cause disability such as:
  - o tendinitis and tendon tearing
  - o peripheral neuropathy;
  - o Central nervous system effects

If you experience any of these undesirable effects during the use of CİPROPOL, stop using it and avoid the use of fluoroquinolone.

- Fluoroquinolone, including CİPROPOL, can cause an exacerbation of muscle weakness in patients with myasthenia gravis . CİPROPOL should be avoided by myasthenia gravis patients.

- Since it is known that fluoroquinolone drugs, including CİPROPOL, are associated with serious side effects, no other alternative can be used in the following indications.
  - o Acute bacterial sinusitis
  - oUncomplicated urinary infection

1. NAME OF MEDICINAL PRODUCT

CİPROPOL 2 mg /ml Solution For I.V. Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient: Contains 2.54 mg ciprofloxacin lactate - equal to 2 mg ciprofloxacin in each ml of infusion solution. 100 ml solution contains 200 mg of ciprofloxacin; 200 ml solution contains 400 mg of ciprofloxacin.

Excipients:

Sodium chloride 9.0 mg/ml

See Part 6.1 for other excipients.

3. PHARMACEUTICAL FORM

Infusion solution

Clear, colorless solution.

pH value of Infusion solutions is between 3,5 and 4,6 ranges.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

In the presence of acute bacterial sinusitis, uncomplicated urinary infection and alternative treatment options, it should not be used due to the risk of serious side effects. In these indications, it can only be used with the approval of an infectious diseases specialist if it is proven with an antibiogram and other alternative treatments cannot be 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* ve *Staphylococcus*.

It is especially indicated in middle ear infections (otitis media) and paranasal sinus infections (sinusitis) induced by gram negative organism or *staphylococcus* including *Pseudomonas aeruginosa.*

• 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 2nd and 3rd 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	Daily and a single dose for adults (mg ciprofloxacin intravenous)	Total duration of treatment (including switch to oral therapy as soon as possible)
Respiratory tract infections (As to severity and organism itself)	2 x 400 mg – 3x 400 mg	7-14 days
Urinary tract infections - Acute, uncomplicated Pyelonephritis - Complicated	 2 x 200 - 400 mg 2 x 400 mg – 3 x 400 mg	 7-21 days 7-21 days

Genital infections - Adnexitis, acute prostatitis, Epididymoorchitis	2 x 400 mg – 3 x 400 mg	14-28 days
Diarrhea	2 x 400 mg	1-5 days
Other infections (see 4.1 Therapeutic indications)	2 x 400 mg	7-14 days
Especially severe and life-threatening infections, For example; - Infections recurring in cystic fibrosis. - Septicemia, especially in the presence of *Pseudomonas*, *Acinetobacter* and *Streptococcus.*	3 x 400 mg	7-14 days
Bone and joint infections For example, Osteomyelitis)	2 x 400 mg – 3x 400 mg	Maximum 3 months (Maximum 2 months in Osteomyelitis)
Patients with immunodepression	2 x 400 mg – 3x 400 mg	During entire neutropenic period
Intra-abdominal infections	2 x 400 mg – 3x 400 mg	5-14 days
Inhalation anthrax (see after being exposed to *Bacillus anthracis)*	2 x 400 mg	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.

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

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.

Route of administration:
Intravenous
Ciprofloxacin 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.

Special populations:

Patient Populations	**Creatine clearance (ml/ms/1.73m^2)**	**Serum creatinine concentration (mg/100 ml)**	**Daily intravenous dose (mg/day)**
Renal failure	30-60	1.4-1.9	800 mg
	< 30	2	400 mg
Renal failure+ Hemodialysis	30-60	1.4-1.9	800 mg (after dialysis)
	< 30	2	400 mg (after dialysis)
Renal failure+ CAPD (continuous ambulatory peritoneal dialysis)	Addition of ciprofloxacin intravenous infusion solution to dialysate (intraperitoneal): 50 mg ciprofloxacin for each liter of dialysate and it is administered 4 times a day in every 6 hours.		
Liver failure	It is not necessary to adjust the dose.		
When together with liver and kidney in question	30-60	1.4-1.9	800 mg
	< 30	2	400 mg

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

Paediatric population:
Cystic Fibrosis:
Clinical and pharmacokinetic data obtained in treatment of acute pulmonary exacerbation based on *P.aeruginosa* infection of cystic fibrosis in pediatric patients with 5-17 years-old has shown that use in intravenous 10 mg/kg dose three times a day (maximum dose 1200 mg) is suitable.

Treatment time in acute pulmonary exacerbations based on *P.aeruginosa* infection of cystic fibrosis in pediatric patients with 5-17 years-old is 10-14 days.

Complicated urinary tract infections and pyelonephritis:
Dose recommended for complicated urinary tract infections or pyelonephritis is intravenous 6-10 mg/kg (maximum dose is 400 mg) within 8 hours.

Treatment time in complicated urinary tract infection and pyelonephritis arising from *E.coli* is 10-21 days.

Inhalation anthrax (seen after being exposed to *Bacillus anthracis)*:
10 mg/kg intravenous dose is administered 2 times a day. Maximum dose administered once a time should not exceed 400 mg. (maximum daily dose is 800 mg).

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.

Total treatment time of inhalation anthrax with ciprofloxacin (i.v. or oral) is 60 days.

Other severe infections:
Three times a day depending on the type of infection 10 mg / kg dose (max. 1200 mg) can be used.

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

4.3. Contraindications
CIPROPOL should not be used 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 is contraindicated since side effects depending on tizanidin clinically may be seen as a result of undesired rise in serum tizanidin

concentration (hypotension, sleepiness, drowsiness) (see 4.5 "Interactions with other medicinal products and other forms of interaction").

4.4. Special warnings and precautions for use

Severe infections and/or severe infections depending on gram positive or anaerobic bacteria:
Ciprofloxacin 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
Ciprofloxacin 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. For genital tract infections, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections
Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the regions. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

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.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and /or international consensus documents regarding the treatment of anthrax.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see: 4.8 undesirable effects). Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.
Required measures should be adopted in use of ciprofloxacin in patients bearing risk in terms of torsade de pointes (for example, QT prolongation, uncorrected hypokalemia) or simultaneously with drugs (for example, class IA or II antiarrhythmic) causing prolongation in QT interval.

Hypoglycemia
As with other quinolones, hypoglycemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended.

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 exacervation (5-17 years) of cystic fibrosis depending on *P. aeruginosa* infections in pediatric patients. Clinical experience is limited for other indications.

Risk/benefit evaluations conducted in relation to inhalation anthrax indication (seen following being exposed to *Bacillus anthracis)* show that use of ciprofloxacin in pediatric patients is suitable. See Part 5.1 Pharmacodymanic Properties Part-Inhalation Anthrax- Additional Information for use dose in pediatric patients in inhalation anthrax indication (seen following being exposed to *Bacillus anthracis)*

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".

Serious potentially irreversible adverse reactions that cause disability, including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects.
Fluoroquinolones, including CİPROPOL, 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, insonmia, severe headache and confusion) (see section 4.8).These reactions can occur within hours or weeks after starting CİPROPOL. Patients of any age group or without pre-existing risk factors experienced these adverse reactions
CİPROPOL should be discontinued immediately if the first signs or symptoms of any serious adverse reaction occur. In addition, the use of fluoroquinolones, including CİPROPOL, should be avoided in patients experiencing any of these serious adverse reactions associated with fluoroquinolones.Epidemiological studies report an increased risk of aortic aneurysm and dissection, especially in the elderly population after the use of fluoroquinolone. 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 only be used 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.

Hypersensitivity

Hypersensitivity and allergic reactions can occur immediately following first administration in some cases. In these cases, physician should be immediately informed.

Anaphylactic/anaphylactoid reactions may very rarely progress up to vital shock. This case can be seen following first administration in some cases. In such cases, ciprofloxacin 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. In such cases, ciprofloxacin 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.

In particular, transaminase, alkaline phosphatase and cholestatic jaundice may increase temporarily in patients with liver damage.

Musculoskeletal system

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

At any sign of tendinitis (e.g. painful swelling, inflammation), should be consulted a doctor and ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Central nervous system (CNS)

It is known that quinolons trigger seizures or seizure threshold. Ciprofloxacin 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 (for example,

low convulsion threshold, anamnesis convulsion reduced cerebral blood flow, structural change in brain, stroke).

Polyneuropathy (alone or in combination with the pain, burning, sensory disorders or neurological symptoms such as muscle weakness) phenomena have been reported in patients with ciprofloxacin.

Central nervous system reactions may emerge just after first administration in some cases. In rare cases, depression or psychosis may escalate in a way that will be dangerous for patient itself. In such cases, ciprofloxacin should be discontinued and physician should be informed immediately.

Skin

It has been shown that ciprofloxacin causes light sensitivity reactions. Thus, patients receiving ciprofloxacin 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).

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 Undesired effects"). Liquid reception in patients taking ciprofloxacin should be regulated well and excessive alkali of urine should be avoided.

In case of renal insufficiency in order to avoid adverse drug effects depends on the accumulation of ciprofloxacin dose adjustment is necessary (Section 4.2).

Hepatobilier system

Hepatic necrosis and life threatening hepatic failure incidents have been reported (See "4.8 Undesired effects"). Treatment should be discontinued in case of symptom and finding of liver disease (anorexia, jaundice, darkening in blood, rash or sensitive abdomen).

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 ciprofloxacin. 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 ciprofloxacin suppresses microbacterial reproduction and may interact with *Mycobacterium spp.* culture test and it may cause incorrect adverse results in samples obtained from patients using ciprofloxacin.

NaCI loading for intravenous formulations

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. 100 ml contains 15,4 mg of sodium chloride.

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 Pointes. Thus, it should not be used in combination with such drugs.

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

Class IA or III antiarrhythmics

Since ciprofloxacin may create additional effect over QT interval, care should be given when it is used in combination with class IA or III antiarrhythmics. 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 ciprofloxacin.

Omeprazole
Administration of ciprofloxacin in combination with therapeutic products containing omeprazole may lead a slight drop in C_{max} and AUC value of ciprofloxacin.

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} rise: 7 times, range: 4-21 times; AUC rise: 10 times, range: 6-24 times). Hypotensive and sedative effects have increased depending on increased serum concentrations. Therapeutic products containing tizanidin should not be administered in combination with ciprofloxacin (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 ")

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 ciprofloxacin 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 ciprofloxacin (See also 4.4. Special warnings and precautions for use).

Phenytoin
Administration of ciprofloxacin and phenytoin at the same time may result with increase or decrease in serum levels of phenytoin and consequently it is recommended to monitor drug 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 ciprofloxacin 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).

Glibenclamide
Use of ciprofloxacin in combination with therapeutic products containing glibeclamide in special cases may increase effect of glibenclamide (hypoglycemia).

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 ").

Ropinirole
In a clinical study, simultaneous use of ropinirole that is a moderate CYP450 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 ciprofloxacin, it is recommended to monitor side effects related to ropinirol and to appropriately adjust dose (See: 4.4 "Special warnings and precautions for use ").

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 ciprofloxacin or just after that (See: 4.4 "Special warnings and precautions for use ").

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 ciprofloxacin is prescribed in combination with sildenafil, risk and benefits should be taken into consideration.

4.6. 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
Since reliability of ciprofloxacin in pregnant women is not identified and drug is likely to create a damage over articular cartilage in immature fetal organism in the basis of animal studies (See: 5.3 Pre-clinical reliability data"), ciprofloxacin is not prescribed to pregnant women.

Lactation
Ciprofloxacin is eliminated to mother's milk. Depending on the risk potential articular damage ciprofloxacin should not be used during breastfeeding (see: 5.3 "Pre-clinical reliability data).

Fertility
Fertility studies in rats:
Fertility is not affected with ciprofloxacin of in-uterus of baby and post-natal development and F1 generation fertility.

Embryotoxicity studies:
Effect of embryotoxicity and teratogenic of ciprofloxacin has not been found.

Prenatal and postnatal development in rats:
It has been seen that there is no effect on prenatal and postnatal development of animals. Histological studies conducted at the end of the process of growth have not signaled any clear sign that baby has undergone any particular damage.

4.7. Effects on ability to use vehicles and machines

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

4.8. Undesired effects

ADR frequencies reported in use of ciprofloxacin are outlined below. Undesired 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, 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, 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)

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

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 and treatment

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

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.

Therefore, antacids containing Mg^{2+} or Ca^{2+} are recommended for monitoring renal function and reducing ciprofloxacin absorption, apart from routine emergency measures.. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

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 a very clinical resistance susceptibility, however, multiple mutations may be resulted with cross resistance generally between clinical ciprofloxacin resistance and quinolon 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
Enterococcus faecalis (several strains are moderately susceptible)
Staphylococcus aureus (susceptible to methicillin)
Staphylococcus saprophyticus

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: "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 μg /ml. In next 12 hours dose, attained average stable state deep point concentration varies between 0.12-0.19 μg /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 μg/ml; average peak serum concentration attained in stable state following administration of intravenous 400 mg ciprofloxacin in each

12 hours is 4.56 µg/ml. Average valley serum concentration in stable state for each two regimes is 0,2 µg/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 µg/ml; valley concentrations vary between 0,09-0,26 µg/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 µg /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 (60 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 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 septicaemia 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, 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 (for pH adjustment)
Water for Injection

6.2. Incompatibilities

0,9% NaCI-containing ciprofloxacin infusion solution is compatible with serum physiological, Ringer solution, Ringer lactate solution, 5% and 10 % glucose solution, 10 % fructose solution, 5 % glucose solution containing 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 ciprofloxacin infusion solutions containing 0,9 % NaCI is 3,5-4,6)

6.3. Shelf life
24 months

6.4. Special precautions for storage
Store at room temperature below 25 C.° Do not cool or freeze.

6.5. Nature and contents of package
CİPROPOL; offered for sale in 100 and 200 ml PP bags. It has 2 forms with and without set.

6.6. Destruction of the residual materials human medicinal product and other special precautions
Unused products or waste materials must be disposaled according to “Medical Waste Control Regulation” and “Packaging and Packaging Waste Control Regulation”.

Preparation for use:
Ciprofloxacin 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.

Instruction for Use:
Solution should be checked before use.
Application is made intravenously with sterile apyrogenic sets.

Only clear, non-particle and sound packaging products should be used.
Application should be commenced within a shortest time after application set is attached to product.

Serial connection should not be made with other infusion liquids for avoiding air embolism likely to occur depending on residual air in bag.

Solution should be applied by using aseptic technique via sterile application set. Liquid should be passed through application set before use in order for avoiding air ingress into system.

Additional drugs may be added before and during infusion with the help of a needle from injection tip under aseptic conditions. Isotonicity of created last product should be identified before performing parenteral application.

Added drug should be mixed wholly with solution before administering it to patient. Solutions containing additional drug should be used just after drug addiction; they should not be kept for later use.

Adding additional drug to solution or incorrect application technique may cause fever reaction depending on pyrogen contamination for product. In case of adverse reaction, infusion should be immediately discontinued.
Single use only.

Partially used solutions should not be stored.
Partially used bags should not be connected to system applied to patients again.

To Open Package
1. Check soundness of outer packaging and whether there is leakage or not; if package is damaged, do not use.
2. Open by tearing off protective outer packaging.
3. Check whether bag inside protective packaging is sound or not by squeezing. Check clarity of solution inside bag and whether there is a foreign material inside or not.

Application preparations:
1. Hang the bag.
2. Remove protective cover at application tip.
3. Stick firmly spike of application set to application tip.
4. Instructions for use of set must be followed for the application of solution to patient.

Adding additional drug:
Caution: As in all parental solutions, all substances to be added to product should be compatible with product. If adding is to be made to product, compatibility should be checked in final mixture before applying it to patient.

Adding drug before application
1. Drug application tip should be disinfected.
2. Drug to be added is added into a bag with injector having a needle in 19-22 gauge thickness.

3. Solution and drug added inside it are well shaken. Tap light application output of bag in heavy drugs such as potassium chloride in upright position and help it to mix well.
Caution: Bags to which additional drug is applied inside should not be stored.

Adding drug during application
1. Clamp of set is closed.
2. Drug application tip should be disinfected.
3. Drug to be added is applied from drug application tip with injector having a needle in 19-22 gauge thickness.
4. Solution is removed from its hanger and reversed.
5. Tap light application outlet and injection inlet of bag while in this position and solution and additional drug are well mixed.
6. Clamp is opened by restoring bag to its old position and application is maintained.

7. MARKETING AUTHORISATION HOLDER

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