# CIPROCEP 250 / 500 MG TABLET

**CONTENT**

***Ciprocep 250mg:*** Each film-coated tablet contains ciprofloxacin hydrochloride 291.5mg (equivalent to ciprofloxacin 250mg).
***Ciprocep 500mg:*** Each film-coated tablet contains ciprofloxacin hydrochloride 583.0mg (equivalent to ciprofloxacin 500mg).

**DESCRIPTION**

***Ciprocep 250mg:*** White, round biconvex film-coated tablets with the letter "TOC" on one side and the figure "250" under a breakline on the other
***Ciprocep 500mg:*** White, oblong-shaped biconvex film-coated tablets with a breakline on one side.

**INDICATION**

Consideration should be given to applicable official guidance on the appropriate use of antibacterial agents.

- Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens:
  - Acute exacerbation of chronic obstructive pulmonary disease including chronic bronchitis*, nosocomial pneumonia/ hospital-acquired pneumonia* – Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by *Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Moraxella catarrhalis, Legionella and Staphylococcus.*
  - Infections of the middle ear (acute otitis media*), acute bacterial rhinosinusitis*, especially if these are caused by gram negative organisms including *Pseudomonas aeruginosa* or by staphylococci.
  - Infections of the eyes
  - Infections of the kidneys and/or the efferent urinary tract (uncomplicated acute cystitis/ uncomplicated cystitis*)
  - Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis
  - Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)
  - Infections of the skin and soft tissue
  - Infections of the bones and joints
  - Septicaemia*
  - Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressant or have neutropenia)
  - Selective intestinal decontamination in immunosuppressed patients

- Prophylaxis of invasive infections due to *Neisseria meningitidis*
  - Children and adolescents – Ciprofloxacin may be used in children for the second- and third-line treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli* (age ranged applied in clinical studies: 1-17 years)

    Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissues.

- Inhalation anthrax (post-exposure) in adults and in children:
  - To reduce the incidence or progression of disease following exposure to aerosolised Bacillus anthracis

* **Ciprocep tablets** should only be used:
- When Pseudomonas is considered AND the patient is allergic to antipseudomonal penicillin/cephalosporins;
- For resistant organism with no other alternative antibiotics available.

**RECOMMENDED DOSE**

Unless otherwise prescribed, the following daily doses are recommended for

**Adults**

| Indication | Recommended |
|---|---|
| Infections of the respiratory tract I (According to severity and organism) | 2 x 500mg to 2 x 750mg |
| Urinary tract infections:<br>- Acute, uncomplicated<br>- Cystitis in women (before menopause)<br>- Complicated | 2 x 250mg to 2 x 500mg<br>Single dose 500mg<br>2 x 500mg to 2 x 750mg |
| Genital infections<br>- Uncomplicated, gonorrhoea (including extragenital sites of infection)<br>- Adnexitis, prostatitis, epididymo-orchitis | 1 x 500mg<br>2 x 500mg to 2 x 750mg |
| Diarrhoea | 2 x 500mg |
| Other infections (see indication) | 2 x 500mg |
| Particularly severe, life threatening infections, i.e.<br>- Recurrent infections in cystic fibrosis<br>- Bone and joint infections<br>- Septicaemia<br>- Peritonitis<br>In particular when Pseudomonas, Staphylococcus or Streptococcus is present | 2 x 750mg |
| Inhalational anthrax (post-exposure) | 2 x 500mg |
| Prophylaxis of invasive infections due to Neisseria meningitides | 1 x 500mg as a single dose |

**Children and adolescents**

| Indications | Recommended |
|---|---|
| Infections in cystic fibrosis | 2 x 20mg/kg body weight (maximum of 750mg per dose) |
| Complicated urinary tract infections and pyelonephritis | 2 x 10mg/kg body weight to 2 x 20mg/kg body weight (maximum of 750mg per dose) |
| Inhalation anthrax (post-exposure) | 2 x 15mg/kg body weight (maximum of 500mg per dose) |

Additional information on special patient population

**Geriatric patients (>65 years)**

Elderly patients should receive a dose as low as possible depending on the severity of their illness and the creatinine clearance.

**Patients with renal and hepatic impairment**

- Patients with renal impairment

| Creatinine Clearance [mL/min/1.73m$^2$] | Serum Creatinine [mg/1000mL] | Total daily dose of ciprofloxacin |
|---|---|---|
| 30 to 60 | 1.4 to 1.9 | Maximum 1000mg |
| Below 30 | ≥ 2.0 | Maximum 500mg |

- Patients with renal impairment on haemodialysis
  - For patients with creatinine clearance between 30 to 60 mL/min/1.73m$^2$ (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100mL, the maximum daily oral dose of ciprofloxacin should be 1000mg
  - For patients with creatinine clearance less than 30mL/min/1.73m$^2$ (severe renal impairment) or serum creatinine concentration equal or higher than 2.0mg/100mL, the maximum daily oral dose of ciprofloxacin should be 500mg.

- Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD)
  - The maximum daily oral dose of ciprofloxacin should be (1 x 500mg Ciprocep film-coated tablet or 2 x 250mg Ciprocep film-coated tablets)

- Patients with hepatic impairment
  - In patients with impairment hepatic function no dose adjustment is required.

- Patients with renal and hepatic impairment
  - For patients with creatinine clearance between 30 and 60mL/min/1.73m$^2$ (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9mg/100mL, the maximum daily oral dose of ciprofloxacin should be 1000mg
  - For patients with creatinine less than 30mL/min/1,73m$^2$ (severe renal impairment) or serum creatinine concentration equal or higher than 2.0mg/100mL, the maximum daily oral dose of ciprofloxacin should be 500mg.

- Children and adolescents
  - Dosing in children with impaired renal and or hepatic function has not been studied.

METHOD OF ADMINISTRATION

- ***Ciprocep tablets*** are to be swallowed whole with a small amount of fluid. It can be taken independently of mealtimes.

- If they are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, ***Ciprocep tablets*** should not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice).
- If patient is unable to take ***Ciprocep tablets*** because of severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration, the treatment can be continued orally.

DURATION OF TREATMENT

- The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms. Mean duration of treatment:
  Adult
  - 1 day for acute uncomplicated gonorrhoea and cystitis
  - Up to 7 days for infections of the kidneys, urinary tract and abdominal cavity
  - Over the entire period of the neutropenic phase in patients with weakened body defences
  - A maximum of 2 months in osteomyelitis
  - And 7 – 14 days in all other infections
- In streptococcal infections, the treatment must last at least 10 days because of the risk of late complications.
- Infections caused by *Chlamydia* spp. should also be treated for a minimum of 10 days.
- Children and adolescents
  - Cystic fibrosis
    For bronchopulmonary infections of cystic fibrosis associated with *Pseudomonas aeruginosa* infection in paediatric patients (aged 5-17 years), duration of treatment is 10-14 days.
  - Complicated urinary tract infections and pyelonephritis
    For complicated urinary tract infections or pyelonephritis due to *Escherichia coli*, the duration of treatment is 10-21 days.
- Inhalation Anthrax (post-exposure) in adults and children
  60 days from the confirmation of *Bacillus anthracis* exposure.

**CONTRAINDICATION**

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients.
- Concomitant administration of ciprofloxacin and tizanidine.

**WARNINGS AND PRECAUTIONS**

- Aortic aneurysm and dissection- Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.
  Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis)
  In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
- The use of Ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolones or fluoroquinolones containing products. Treatment of these patients with Ciprofloxacin should be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.
- Severe infections and mixed infections with Gram-positive and anaerobic pathogens – Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections, ciprofloxacin must be co-administered with other appropriate antibacterial agents.
- Streptococcal Infections (including Streptococcus pneumoniae) – Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.
- Genital tract infections- Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone resistant Neisseria gonorrhoeae isolates. Therefore, ciprofloxacin should be administered for the treatment of gonococcal urethritis or cervicitis only if ciprofloxacin resistant Neisseria gonorrhoeae can be excluded. For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should be considered in combination with another appropriate antibacterial agent (e.g. 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 European Union. Prescribers are advised to take into account the local prevalence of resistance in Escherichia coli to fluoroquinolones. The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of Escherichia coli to quinolones.
- Intra-abdominal infections- There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.
- Travellers' diarrhoea – The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.
- Infections of the bones and joints- Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the 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.
- Paediatric population- The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who have experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.
  Broncho-pulmonary infections in cystic fibrosis- clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.
  Complicated urinary tract infection and pyelonephritis- Ciprofloxacin treatment of urinary infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
  Other specific severe infections- Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify ciprofloxacin use.
  The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.
- Hypersensitivity – Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
- 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.
  Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
  At first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroid should not be used if signs of tendinopathy occur.
- Ciprofloxacin should be used in caution in patients with myasthenia gravis, because symptoms can be aggravated - Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis.
- Vision disorder – If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
- Photosensitivity – Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

- Central nervous system – Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued. Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideation/thought culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.
- Cardiac disorders – 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 antiarrhythmic, 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 population.
- Dysglycaemia – As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.
- Gastrointestinal system – The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment. In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.
- Renal and urinary system – Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.
- Impaired renal function – Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.
- Hepatobiliary system – Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.
- Glucose-6-phosphate dehydrogenase deficiency – Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.
- Resistance – During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated with or without a clinical apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudomonas species.
- Cytochrome P450 – Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. theophylline) may be necessary.
- Methotrexate – The concomitant use of ciprofloxacin with methotrexate is not recommended.
- Interaction with tests – The in-vitro activity of ciprofloxacin against Mycobacterium tuberculosis might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.
- Peripheral neuropathy – Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolone or fluoroquinolones. Patients under treatment with ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition.
- Prolonged disabling and potentially irreversible serious adverse drug reactions: Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contract their prescriber for advice.

**DRUG INTERACTIONS**

**Effects of other products on ciprofloxacin:**

- Drugs known to prolong QT interval
  Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III antiarrhythmic, tricyclic antidepressants, macrolides, antipsychotics)

- Chelation complex formulation
  The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids and highly buffered drugs (e.g. didanosine tablets), containing magnesium, aluminium or calcium reduce the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before, or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of $H_2$ receptor blockers.

- Food and dairy products
  Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or minerals-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.

- Probenecid
  Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

- Metoclopramide
  Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

- Omeprazole
  Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of $C_{max}$ and AUC of ciprofloxacin.

**Effects of ciprofloxacin on other medicinal products:**

- Tizanidine
  Tizanidine must not be administered together with ciprofloxacin. There was an increased in serum tizanidine concentration when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

- Methotrexate
  Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate associated toxic reactions. The concomitant use is not recommended.

- Theophylline
  Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

- Other xanthine derivatives
  On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentoxifylline), raised serum concentrations of these xanthine derivatives were reported.

- Phenytoin
  Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

- Ciclosporin
  A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

- Vitamin K antagonists
  Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ration) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

- Duloxetine
  Concomitant use of duloxetine with strong inhibitors of the CYP450 1 A2 isozyme such as fluvoxamine may result increase of AUC and $C_{max}$ of duloxetine. No clinical data available on possible interaction with ciprofloxacin, however, similar effects may occur upon concomitant administration.

- Ropinirole
  Concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the $C_{max}$ and AUC of ropinirole. Monitoring of ropinirole-related side effects and dose adjustments as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

- Lidocaine
  Concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 isozyme, reduces clearance of intravenous lidocaine. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

- Clozapine
  Following concomitant administration of 250mg Ciprofloxacin for 7 days, serum concentration of clozapine and N-desmethylclozapine were increased. Appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

- Sevelamer
  The bioavailability of ciprofloxacin is reduced by the concomitant administration with sevelamer. Therefore, it is recommended that the two should not be taken concomitantly

- Sildenafil
  $C_{max}$ and AUC of sildenafil were increased approximately 2-fold after an oral dose of sildenafil given concomitantly with ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

- Agomelatine
  It was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration.

- Zolpidem
  Co-administration of ciprofloxacin may increase blood levels of zolpidem; concurrent use is not recommended.

**PREGNANCY AND LACTATION**

• Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animal exposed to quinolones, effects on immature cartilage have been observed thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism/foetus. As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

• Breast-feeding

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

**SIDE EFFECTS**

| System organ class | Frequency | Preferred term |
|---|---|---|
| Infections and infestations | Uncommon | Mycotic superinfections |
| | Rare | Antibiotic associated colitis (very rarely with possible fatal outcome) |
| Blood and lymphatic system disorders | Uncommon | Eosinophilia |
| | Rare | Leukopenia, anaemia, neutropenia, leucocytosis, thrombocytopenia, thrombocythemia |
| | Very rare | Haemolytic, anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening) |
| Endocrine disorders | Frequency not known | Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) |
| Immune system disorders | Rare | Allergic reaction, allergic oedema/angioedema |
| | Very rare | Anaphylactic reaction, anaphylactic shock (life-threatening), serum sickness-like reaction |
| Metabolism and nutrition disorder | Uncommon | Decreased appetite and food intake |
| | Rare | Hyperglycaemia, hypoglycaemia |
| Psychiatric disorders* | Uncommon | Psychomotor hyperactivity / agitation |
| | Rare | Confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in suicidal ideation/thoughts or suicide attempts and completed suicide), hallucination |
| | Very rare | Psychotic reactions (potentially culminating in suicidal ideations/thought or suicide attempts and completed suicide) |
| | Frequency not known | Mania, hypomania |
| Nervous system disorders* | Uncommon | Headache, dizziness, sleep disorders, taste disorders |
| | Rare | Par-and dysesthesia, hypoesthesia, tremor, seizures (including status epilepticus), vertigo |
| | Very rare | Migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial hypertension and pseudotumor cerebri |
| | Frequency not known | Peripheral neuropathy and polyneuropathy |
| Eye disorders* | Rare | Visual disturbance |
| | Uncommon | Visual colour distortions |
| Ear and labyrinth disorders* | Rare | Tinnitus, hearing loss / hearing impaired |
| Cardiac disorders | Rare | Tachycardia |
| | Frequency not known | Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged |
| Vascular disorders | Rare | Vasodilatation, hypotension, syncope |
| | Very rare | Vasculitis |
| Respiratory, thoracic and mediastinal disorders | Rare | Dyspnoea (including asthmatic condition) |
| Gastrointestinal disorders | Common | Nausea, diarrhoea |
| | Uncommon | Vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence |
| | Rare | Antibiotic associated diarrhoea including pseudomembranous |

| | | |
|---|---|---|
| | | colitis (very rarely with possible fatal outcome) |
| | Very rare | Pancreatitis |
| Hepatobiliary disorders | Uncommon | Increase in transaminases, increased bilirubin |
| | Rare | Hepatic impairment, cholestatic icterus, hepatitis |
| | Very rare | Liver necrosis (very rarely progressing to life-threatening hepatic failure) |
| Skin and subcutaneous tissue disorders | Uncommon | Rash, pruritus, urticaria |
| | Rare | Photosensitivity reaction, blistering |
| | Very rare | Petechiae, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening) |
| | Frequency not known | Acute generalised exanthematous pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) |
| Musculoskeletal, connective tissue and bone disorders* | Uncommon | Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia |
| | Rare | Myalgia, arthritis, increased muscle tone and cramping |
| | Very rare | Muscular weakness, tendinitis, tendon rupture (predominantly Achilles tendon), exacerbation of symptoms of myasthenia gravis |
| Renal and urinary disorders | Uncommon | Renal impairment |
| | Rare | Renal failure, haematuria, crystalluria, tubulointerstitial nephritis |
| General disorders and administration site conditions* | Uncommon | Asthenia, fever, unspecific pain, feeling unwell |
| | Rare | Oedema, sweating (hyperhidrosis) |
| | Very rare | Gait disturbance |
| Investigations | Uncommon | Increased in blood alkaline phosphatase |
| | Rare | Prothrombin level abnormal, Increased amylase |
| | Frequency not known | International normalised ratio increased (in patients treated with Vitamin K antagonists) |

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see section Warning and Precautions).

**SYMPTOMS AND TREATMENT OF OVERDOSE**

• An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16g has been reported to cause acute renal failure. Symptoms of overdose may include dizziness, tremor, headaches, 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 e.g. ventricular emptying followed by medical carbon. It is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.

• Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses. 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.

**EFFECTS ON ABILITY TO DRIVE AND USE MACHINES**

The ability to drive or operate machinery may be impaired by Ciprofloxacin especially so when alcohol is taken concurrently.

**PHARMACODYNAMICS**

Activity:
Ciprofloxacin is a synthetic 4-quinolone derivative antibacterial agent of the fluoroquinolone class.

Mechanism of action:
As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Spectrum of activity:
**Susceptibility**
The prevalence of the acquired resistances can vary for some species geographically and with time. Therefore, it is important to obtain information on local resistance patterns, particularly when treating more severe infections.
The information provided below gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

**Groupings of relevant species according to ciprofloxacin susceptibility:**

| ORGANISM | PREVALENCE OF RESISTANCE |
|---|---|
| **Sensitive** | |
| **Gram-positive bacteria** | |
| *Staphylococcus aureus* (methicillin sensitive) | 0-14% |
| *Streptococcus agalactiae* | 0-17% |
| **Gram-negative bacteria** | |
| *Acinetobacter baumannii* | 6-93% |
| *Acinetobacter* spp. | 14-70% |
| *Aeromonas hydrophila* | |
| *Campylobacter jejuni/coli* | 0-82% |
| *Citrobacter freundii* | 0-4% |
| *Enterobacter aerogenes* | |
| *Enterobacter cloacae* | 0-3% |
| *Enterobacter* spp | 3-13% |
| *Escherichia coli* | 2-7% |
| *Haemophilus influenzae* | 0-1% |
| *Klebsiella spp.* | 2-21% |
| *Moraxella catarrhalis* | |
| *Morganella morganii* | 1-2% |
| *Neisseria gonorrhoeae* | 5% |
| *Plesiomonas shigelloides* | |
| *Proteus mirabilis* | 0-10% |
| *Proteus vulgaris* | 4% |
| *Providencia spp.* | 4% |
| *Pseudomonas aeruginosa* | 1-28% |
| *Salmonella spp.* | |
| *Salmonella typhi* | 0-2% |
| *Serratia liquefaciens* | |
| *Serratia marcescens* | 23% |
| *Shigella spp* | |
| *Vibrio spp* | |
| *Yersinia enterocolitica* | |
| **Anaerobes*** | |
| *Peptococcus spp.* | - |
| *Peptostreptococcus spp.* | - |
| *Veillonella parvula* | - |
| **Other pathogens** | |
| *Legionella pneumophila* | - |
| Intermediate | |
| *Viridans streptococci* | 5-9% |
| *Streptococcus pneumonziae* | 2.8% |
| *Streptococcus pyogenes* | 2.8% |
| **Other pathogens** | |
| *Chlamydia spp* | - |
| **Resistant** | |
| **Gram-positive aerobes** | |
| *Enterococcus spp* | - |
| *Staphylococcus aureus* (methicillin resistant) | 48-90% |
| **Gram-negative aerobes** | |
| *Stenotrophomonas maltophila* | - |
| *Flavobacterium menmgosepticum* | - |

| | |
|---|---|
| *Nocardia asteroides* | - |
| **Anaerobes** | |
| *Bacteroides fragilis* | - |
| *Bacteroides thetaiotaomicron* | - |
| *Clostridium difficile* | - |

* Ciprofloxacin is not considered the drug of first choice for treatment of infections with anaerobes.

In-vitro investigations have shown that resistance to ciprofloxacin is commonly due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the class. Impermeability and/or drug efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various drugs within the class and the affinity of transport systems for each drug.

**PHARMACOKINETICS**

- Absorption:
  After oral administration, ciprofloxacin is predominantly absorbed from the duodenum and upper jejunum, and reaches peak serum concentrations within 60-90 min. After single dose of 250mg and 500mg $C_{max}$ values are about 0.8-2.0mg/1 and 1.5-2.9mg/1 respectively.
  The absolute bioavailability is approximately 70 to 80% $C_{max}$- and AUC-values are proportionally increased with the dose.
  Food intake has no effect on the plasma concentration profile of ciprofloxacin.

- Distribution:
  The steady-state volume of distribution of ciprofloxacin is 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma in non-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravasal space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.

- Metabolism/Elimination:
  Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5ml/min/kg, and total clearance amounts to 8-10ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.
  Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 show antibacterial activity comparable with or smaller than nalidixic acid. M4 with the lowest quantity, has an antimicrobial activity very much corresponding to norfloxacin.

Excretion after oral administration (in % of the ciprofloxacin dose):

| | Urine | Faeces |
|---|---|---|
| Ciprofloxacin | 44.7 | 25.0 |
| Metabolites | 11.3 | 7.5 |

The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral administration.
Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renal function must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

**EXCIPIENTS**

Lactose, sodium lauryl sulfate, povidone K30, sodium starch glycolate, magnesium stearate, hydroxypropyl methylcellulose 2910 (E5), hydroxypropyl methycellulose 2910 (E15), titanium dioxide, talc, polyethylene glycol 6000.

**PACKING / PACK SIZE**

***Ciprocep 250mg:***
1) Aluminium foil strip of 10 tablets per strip. Box of 10 strips and 50 strips.
***Ciprocep 500mg:***
1) Aluminium foil strip of 10 tablets per strip. Box of 10 strips.
2) Alu-PVC blister strip of 10 tablets per strip. Box of 10 strips and 50 strips.

**STORAGE CONDITION**

Do not store above 30°C.
Protect from light.
Keep out of reach of children.
*Jauhi daripada kanak-kanak.*

Shelf life: Please refer to the outer box label.

**MANUFACTURED BY:**

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