# Ciproxsel Tablet/Infusion

( C i p r o f l o x a c i n U S P )

**COMPOSITION**

**Ciproxsel Tablet 250mg**
Each film coated tablet contains:
Ciprofloxacin hydrochloride (USP) eq. to Ciprofloxacin.....250mg
**Ciproxsel Tablet 500mg**
Each film coated tablet contains:
Ciprofloxacin hydrochloride (USP) eq. to Ciprofloxacin.....500mg
**Ciproxsel Tablet 750mg**
Each film coated tablet contains:
Ciprofloxacin hydrochloride (USP) eq. to Ciprofloxacin.....750mg
**Ciproxsel Infusion 200mg/100ml**
Each 100ml vial contains:
Ciprofloxacin lactate (MS) eq. to Ciprofloxacin.....200mg
**Product complies USP specs.**

**DESCRIPTION**

Ciprofloxacin is a second generation fluoroquinolone antibacterial agent that inhibits the supercoiling activity of bacterial DNA gyrase, halting DNA replication.

**MECHANISM OF ACTION**

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

**MECHANISM OF RESISTANCE**

*In-vitro* resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.
Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates.
Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility.

**INDICATIONS**

***Adults***
- Lower respiratory tract infections due to Gram-negative bacteria.
- Exacerbations of chronic obstructive pulmonary disease.
- Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis.
- Pneumonia.
- Chronic suppurative otitis media.
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria.
- Urinary tract infections.
- Gonococcal uretritis and cervicitis.
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae.*
- Pelvic inflammatory disease including cases *due to Neisseria gonorrhoeae.*

*In the above genital tract infections when thought or known to be due to Neisseria gonorrhoeae it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.*
- Infections of the gastro-intestinal tract (e.g. travellers, diarrhea).
- Intra-abdominal infections.
- Infections of the skin and soft tissue caused by Gram-negative bacteria.
- Malignant external otitis.
- Infections of the bones and joints.
- Treatment of infections in neutropenic patients.
- Prophylaxis of infections in neutropenic patients.
- Prophylaxis of invasive infections due to *Neisseria meningitidis.*
- Inhalation anthrax (post-exposure prophylaxis and curative treatment).

***Children and adolescents***
- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa.*
- Complicated urinary tract infections and pyelonephritis.
- Inhalation anthrax (post-exposure prophylaxis and curative treatment).

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.
Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

**DOSAGE AND ADMINISTRATION**

***Adults***

| Indications | Daily dose in mg | Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin) | |
|---|---|---|---|
| Infections of the lower respiratory tract | 500 mg twice daily to 750 mg twice daily | 7 to 14 days | |
| Infections of the upper respiratory tract | Acute exacerbation of chronic sinusitis | 500 mg twice daily to 750 mg twice daily | 7 to 14 days |
| | Chronic suppurative otitis media | 500 mg twice daily to 750 mg twice daily | 7 to 14 days |
| | Malignant external | 750 mg twice daily | 28 days up to 3 months |
| Urinary tract infection | Uncomplicated cystitis | 250 mg twice daily to 500 mg twice daily | 3 days |
| | | In pre-menopausal women, 500 mg single dose may be used. | |
| | Complicated cystitis, Uncomplicated pyelonephritis | 500 mg twice daily | 7 days |
| | Complicated pyelonephritis | 500 mg twice daily to 750 mg twice daily | at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses) |
| | Prostatitis | 500 mg twice daily to 750 mg twice daily | 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |
| Genital tract infections | Gonococcal uretritis and cervicitis | 500 mg as a single dose | 1 day (single dose) |
| | Epididymo-orchitis and pelvic inflammatory diseases | 500 mg twice daily to 750 mg twice daily | at least 14 days |
| Infections of the gastro-intestinal tract and intraabdominal infections | Diarrhea caused by bacterial pathogens including Shigella spp. other than Shigella dysenteriae type 1 and empirical treatment of severe travellers' diarrhea | 500 mg twice daily | 1 day |
| | Diarrhea caused by Shigella dysenteriae type 1 | 500 mg twice daily | 5 days |
| | Diarrhea caused by Vibrio cholerae | 500 mg twice daily | 3 days |
| | Typhoid fever | 500 mg twice | daily 7 days |
| | Intra-abdominal | 500 mg twice daily to | 5 to 14 days |
| | infections due to Gram-negative bacteria | 750 mg twice daily | |
| Infections of the skin and soft tissue | 500 mg twice daily to 750 mg twice daily | 7 to 14 days | |
| Bone and joint infections | 500 mg twice daily to 750 mg twice daily | Max. of 3 months | |
| Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance. | 500 mg twice daily to 750 mg twice daily | Therapy should be continued over the entire period of neutropenia | |
| Prophylaxis of invasive infections due to Neisseria meningitidis | 500 mg as a single dose | 1 day (single dose) | |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure. | 500 mg twice daily | 60 days from the confirmation of Bacillus anthracis exposure | |

***Children and adolescents***

| Indications | Daily dose in mg | Total duration of treatment (potentially including initial parenteral treatment |
|---|---|---|
| Cystic fibrosis | 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 14 days |
| Complicated urinary tract infections and pyelonephritis | 10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose. | 10 to 21 days |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically | 10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose. | 60 days from the confirmation of Bacillus anthracis exposure |
| appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure. | | |
| Other severe infections | 20 mg/kg body weight twice daily with a maximum of 750 mg per dose | According to the type of infections |

***Geriatric patients***
Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.
***Renal and hepatic impairment***
*Recommended starting and maintenance doses for patients with impaired renal function:*

| Creatinine Clearance [mL/min/1.73 m²] | Serum Creatinine [µmol/L] | Oral Dose [mg] |
|---|---|---|
| > 60 | < 124 | See Usual Dosage. |
| 30-60 | 124 to 168 | 250-500 mg every 12h |
| < 30 | > 169 | 250-500 mg every 24h |
| Patients on hemodialysis | > 169 | 250-500 mg every 24h (after dialysis) |
| Patients on peritoneal dialysis | > 169 | 250-500 mg every 24h |

In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired renal and/or hepatic function has not been studied.

**Method of IV administration**

Ciprofloxacin should be checked visually prior to use. It must not be used if cloudy. Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, infusion time is also 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

**PHARMACOKNETICS**

**Absorption**

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. The absolute bioavailability is approximately 70-80%.
Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously. Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites. A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC). A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC. The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a $C_{max}$ similar to that observed with a 750 mg oral dose. A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

**Distribution**

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

**Metabolism**

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

**Elimination**

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.
Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 h.
Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

**WARNINGS AND PRECAUTIONS**

**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 coadministered 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***
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae.
Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

***Intra-abdominal infections***
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

***Travellers' diarrhea***
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.

***Children and adolescents***
The use of ciprofloxacin in children and adolescents should follow available official guidance.
Ciprofloxacin treatment should be initiated only by physicians who are 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 infections and pyelonephritis***
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

***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 a 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 Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids. At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest. Ciprofloxacin should be used with caution in patients with myasthenia gravis.

***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***
Quinolones are known to trigger seizures or lower the seizure threshold. 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 self-endangering behaviour. In these cases, ciprofloxacin should be discontinued. Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

***Cardiac disorders***
Since ciprofloxacin is associated with cases of QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

***Gastrointestinal System***
The occurrence of severe and persistent diarrhea 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.

***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***
Hemolytic 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 clinically 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, ropinirole, tizanidine). 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. of 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.

**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 animals 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 /fetus. As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

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

**SIDE EFFECTS**

**Infections and Infestations**
Mycotic Superinfections, Antibiotic associated colitis (very rarely with possible fatal outcome)

**Blood and Lymphatic System Disorders**
Eosinophilia, leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia, haemolytic anaemia, agranulocytosis, pancytopenia (life threatening), bone marrow depression (life threatening).

**Immune System Disorders**
Allergic reaction, allergic edema, angioedema, anaphylactic reaction, anaphylactic shock (life threatening), serum sickness like reaction.

**Metabolism and Nutrition Disorders**
Anorexia, Hyperglycaemia.

**Psychiatric Disorders**
Psychomotor hyperactivity, agitation, confusion and disorientation, anxiety reaction, abnormal dreams, depression, hallucinations, psychotic reactions.

**Nervous System Disorders**
Headache, dizziness, sleep disorders, taste disorders, par- and dysaesthesia, hypoaesthesia, tremor, seizures, vertigo, migraine, disturbed coordination, gait disturbance, olfactory nerve disorders, intracranial, hypertension, peripheral neuropathy.

**Eye Disorders**
Visual disturbances, visual color distortions.

**Ear and Labyrinth Disorders**
Tinnitus, Hearing loss, Hearing impaired.

**Cardiac Disorders**
Tachycardia, Ventricular arrhythmia, QT prolongation, torsades de pointes.

**Vascular Disorders**
Vasodilatation, Hypotension, Syncope, Vasculitis

**Respiratory, Thoracic and Mediastinal Disorders**
Dyspnea (including asthmatic condition)

**Gastrointestinal Disorders**
Nausea, diarrhea, vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence, pancreatitis.

**Hepatobiliary Disorders**
Increase in transaminases, increased bilirubin, hepatic impairment, cholestatic icterus, hepatitis, liver necrosis (very rarely progressing to life-threatening hepatic failure).

**Skin and Subcutaneous Tissue Disorders**
Rash, pruritus, urticaria, photosensitivity reactions, petechiae, erythema multiforme, erythema nodosum, stevens-johnson syndrome (potentially life threatening), toxic epidermal necrolysis (potentially life threatening).

**Musculoskeletal, Connective Tissue and Bone Disorders**
Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthralgia, myalgia, arthritis, increased muscle tone and cramping, muscular weakness, tendinitis, tendon rupture (predominantly achilles tendon), exacerbation of symptoms of myasthenia gravis.

**Renal and Urinary Disorders**
Renal impairment, renal failure, haematuria, crystalluria, tubulointerstitial nephritis

**General Disorders and Administration Site Conditions**
Asthenia, fever, edema, sweating, (hyperhidrosis)

**Investigations**
Increase in blood alkaline phosphatase, prothrombin level, abnormal increased amylase.

**DRUG INTERACTIONS**

**Chelation Complex Formation**
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 reduces 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 H2 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 mineral-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.

**Tizanidine**
Tizanidine must not be administered together with ciprofloxacin . In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration ($C_{max}$ increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) 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 serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely 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 (oxpentifylline), 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.

**Oral anticoagulants**
Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

**Ropinirole**
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of $C_{max}$ and AUC of ropinirole by 60% and 84%, respectively.

**Clozapine**
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively.

**CONTRAINDICATIONS**

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

**STORAGE & INSTRUCTIONS**
Store between 15-25°C.
Protect from heat, sunlight and moisture
Keep away from the reach of children.
To be sold on the prescription of a registered medical practitioner only.

**HOW SUPPLIED**

**Ciproxsel Tablet 250mg**
10's, 10x10's tablets.

**Ciproxsel Tablet 500mg**
10's, 10x10's tablets.

**Ciproxsel Tablet 750mg**
10's tablets.

**Ciproxsel Infusion 200mg/100ml**
100ml vial.

Manufactured by:
**PHARMASOL**
**PRIVATE LIMITED**
Plot # 549,Sundar Industrial Estate,
Lahore, Pakistan.