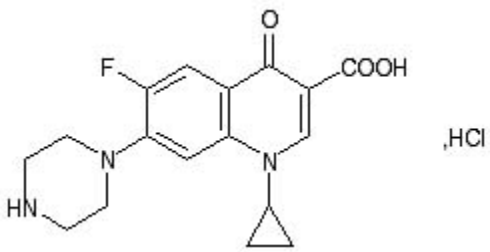
PRODUCT INFORMATION
CIPROFLOXACIN SANDOZ® 250 MG, 500 MG & 750 MG FILM-COATED TABLETS

NAME OF THE MEDICINE

Ciprofloxacin hydrochloride

1-cyclopropyl- 6-fluoro-1,4-dihydro-4-oxo-7-(piperazin-1-yl)quinoline-3 -carboxylic acid (as the monohydrochloride monohydrate salt)



H_2O

CAS [86393-32-0]

Empirical formula: $C_{17}H_{18}FN_3O_3.HClxH_2O$ MW: 385.8

DESCRIPTION

It is a pale yellow, crystalline powder, soluble in water, slightly soluble in methanol, very slightly soluble in ethanol, practically insoluble in acetone, in ethyl acetate and in methylene chloride.

In addition to ciprofloxacin hydrochloride, Ciprofloxacin Sandoz tablets also contain colloidal anhydrous silica, povidone, magnesium stearate, microcrystalline cellulose, stearic acid, sodium starch glycollate type A, croscarmellose sodium, hypromellose, macrogol 6000, talc, and titanium dioxide.

PHARMACOLOGY

Ciprofloxacin is a synthetic carboxyquinolone derivative, with a broad spectrum antimicrobial activity.

Pharmacodynamics

Microbiology:
Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interference with the enzyme DNA gyrase. Ciprofloxacin is usually active against the following organisms *in vitro*:

Gram-negative. Escherichia coli; Klebsiella sp. (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* sp.; *Citrobacter* sp.; *Salmonella* sp.; *Shigella* sp.; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* sp. (including *Serratia marcescens*); *Pseudomonas aeruginosa*; *Pseudomonas fluorescens*; *Campylobacter* sp.; *Haemophilus influenzae*; *Neisseria gonorrhoeae*; *Moraxella (Branhamella) catarrhalis*.

Gram-positive. Staphylococcus aureus (including methicillin susceptible and methicillin resistant strains); coagulase negative *Staphylococcus* sp. (including *Staphylococcus epidermidis*); *Streptococcus pyogenes* (group A); *Streptococcus pneumoniae*; *Enterococcus faecalis.*

Note. Gram-positive organisms are generally less sensitive to ciprofloxacin than Gram-negative organisms.

Most strains of Streptococci are only moderately susceptible to ciprofloxacin. Clinical studies have shown the medicine to be effective for urinary tract infections caused by *Enterococcus faecalis*; however failures and reinfections have been observed with prostatitis. Although bronchial infections caused by *Strep. pneumoniae* and skin infections caused by *Strep. pyogenes* have been shown to respond to ciprofloxacin, it is not the medicine of first choice in such infections, particularly *Strep. pneumoniae* infection of the lower respiratory tract.

Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin, as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile.*

Enterococcus faecium, Ureaplasma urealyticum and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.

The *in vitro* minimal inhibitory concentration (MIC) of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe

infections. This information gives only an approximate guidance whether microorganisms will be susceptible for ciprofloxacin or not."

Ciprofloxacin has been shown to be active against *Bacillus anthracis* both in vitro and by use of serum levels as a surrogate marker

Ciprofloxacin is less active when tested at acidic pH, and its antibacterial activity may be reduced by up to 100-fold in acidic urine. The inoculum size has little effect when tested *in vitro*. The minimal bactericidal concentration (MBC) is generally two to eight times the MIC.

Resistance to ciprofloxacin *in vitro* develops slowly (multiple step mutation). Rapid one step development of resistance has not been observed. However, in practice, resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *P. aeruginosa* infections, especially in patients with cystic fibrosis, and in *S. aureus* infections.

Ciprofloxacin does not exhibit cross resistance with nonquinolone antibacterial agents, e.g. Beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g. nalidixic acid, cinoxacin) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that when ciprofloxacin is combined with other antimicrobial agents, particularly beta-lactams, the combination behaves either in an indifferent or additive manner. Synergism or antagonism have, however, been observed rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciprofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility tests:
Dilution or diffusion techniques- either quantitative (MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (eg NCCLS). Standardised susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible medicines, the test should be repeated. This category implies possible clinical applicability in body sites where the medicine is physiologically concentrated or in situations where high dosage of medicine can be used. This category also provides a buffer zone, which prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the

antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note. The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

Pharmacokinetics

Absorption
Ciprofloxacin tablets are rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first-pass metabolism. Co-administration of ciprofloxacin with food appears to lower peak serum levels and delay the absorption of ciprofloxacin, resulting in peak concentrations closer to 2 hours after dosing rather than 1 hour. The overall absorption, however, is not substantially affected. Absorption also appears to be greatly reduced by prior administration of antacids

Distribution
After oral dosing, ciprofloxacin is widely distributed throughout the body. The binding of ciprofloxacin to serum proteins is 20 to 40%. Serum concentrations increase in a dose proportional manner and were, after multiple doses, as shown in Table 1:

Table 1
Ciprofloxacin Sandoz serum concentration after oral dosing

Dose (mg)	Maximum serum concentration (µg/mL)	Area under curve (AUC) (µg.hour/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained one to two hours after oral dosing. Mean concentrations twelve hours after dosing with 250, 500 or 750mg are 0.1, 0.2 and 0.4 microgram/mL respectively.

Metabolism
Ciprofloxacin is also metabolised. Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Elimination
The serum elimination half-life in subjects with normal renal function is approximately four hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first two hours after an oral dose of 250mg, the urine concentration of ciprofloxacin usually exceeds 200 microgram/mL. Eight to twelve hours after the same dose, urine levels are approximately 30 microgram/mL. Urinary excretion

of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18L/hour which exceeds the normal glomerular filtration rate of 7.2L/hour. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21-40 mL/min, the half-life of ciprofloxacin is only slightly prolonged. Dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half-life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see DOSAGE AND ADMINISTRAT ION).

Although bile concentrations of ciprofloxacin are three to four times higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile. Approximately 20 to 35% of an oral dose is recovered from the faeces within five days after dosing.

INDICATIONS

Treatment of infections caused by susceptible organisms in the following conditions:
Urinary tract infections, gonorrhoeal urethritis and cervicitis, gastroenteritis, bronchial infections, skin and skin structure infections, bone and joint infections, chronic bacterial prostatitis of mild to moderate severity.

Note. Typhoid and paratyphoid infections and infections due to multiresistant *S. aureus* are excluded from the above due to insufficient data, because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the medicine of choice in cases with Gram-positive infections, such as pneumonia due to *S. pneumoniae.*

Chronic bacterial prostatitis should be demonstrated by microbiological evidence localising infection to the prostate.

Strains of *N. gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

Appropriate culture and susceptibility tests should be performed before treatment in order to determine organism susceptibility to ciprofloxacin and after treatment as warranted by the clinical condition. Therapy with Ciprofloxacin Sandoz may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Ciprofloxacin Sandoz is suitable to treat mixed infections caused by susceptible strains of both Gram-negative and Gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiological agents, additional therapy should be considered.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or other quinolones, including nalidixic acid or any of the excipients, is a contraindication to its use.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine induced side effects (hypotension, somnolence, drowsiness) can occur.

PRECAUTIONS

Streptococcus pneumoniae infections
Ciprofloxacin is not recommended for treatment of pneumococcal infections due to inadequate efficacy against Streptococcus pneumoniae.

Antibiotic associated colitis:
Antibiotic associated colitis has been rarely reported with ciprofloxacin, but it should be considered in patients who develop diarrhoea.

Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to medicine discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Medicines which delay peristalsis such as; opiates and diphenoxylate with atropine (Lomotil®), may prolong and/or worsen the condition and should not be used.

Cardiac disorders:
Ciprofloxacin is associated with cases of QT prolongation. In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Women may also be more sensitive to QT prolongation medicine compared to men as they tend to have a longer baseline QTc interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) or in patients with risk factors for torsade de pointes (e.g. known QT prolongation, uncorrected electrolyte imbalance such as hypokalemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Effects on the Liver
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 (see ADVERSE EFFECTS). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin.

Effects on tendons:
Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. This may occur even within the first 48 hours of treatment or up to several months after discontinuation of ciprofloxacin. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Therapy should be discontinued if the patient experiences any signs of tendonitis (e.g. pain swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to the increased risk of tendon rupture.

Superinfections:
As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of nonsusceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Pseudomonas aeruginosa infections in cystic fibrosis:
Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *P. aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *P. aeruginosa* infections in cystic fibrosis patients following a single course of the medicine.

Anaphylactoid reactions:
In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately.
Serious, and occasionally fatal, anaphylactoid reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). In these cases Ciprofloxacin Sandoz should be discontinued and appropriate medical treatment given.

Phototoxicity:
Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Effects on the central nervous system (CNS):
As with other quinolones, ciprofloxacin may cause CNS stimulation which may lead to transient tremor, restlessness, lightheadedness, confusion and very rarely to hallucinations or convulsive seizures. Ciprofloxacin should be used with caution in patients with CNS disorders, such as severe cerebral arteriosclerosis or epilepsy.

In some instances, the CNS reactions may occur after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts and self-endangering behavior such as attempted or completed suicide. In these cases, ciprofloxacin has to be discontinued and the physician should be informed immediately.

Epileptic patients:
Ciprofloxacin, like other fluoroquinolones is known to trigger seizures or lower seizure threshold. Ciprofloxacin should be used with caution in epileptics and in patients who have suffered from previous CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central nervous side effects. Cases of status epilepticus have been reported. If seizures occur, Ciprofloxacin should be discontinued.

Nervous system:
Ciprofloxacin might exacerbate symptoms of myasthenia gravis. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a doctor should be consulted.
Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. 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 (see ADVERSE EFFECTS).

Vision disorders:
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see ADVERSE EFFECTS).

Cytochrome P450:
Ciprofloxacin is known to be a moderate inhibitor of the CYP450 1A2 enzymes. Care should be taken when other medicines are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, clozapine, olanzapine, ropinirole). Increased plasma concentrations associated with medicine specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. (See also PRECAUTIONS, Interactions with other medicines).

Crystalluria:
The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the medicine, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Impaired renal function:
Alteration of the dosage regimen is necessary for patients with impairment of renal function (see DOSAGE AND ADMINISTRATION).

Impaired hepatic function:
There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Use in pregnancy
Australian pregnancy Category B3 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

Reproduction studies have been performed in rats and mice at doses up to 100mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and intravenous doses of up to 30mg/kg and have revealed no evidence of impaired fertility or harm to the foetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intrauterine deaths and foetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20mg/kg, no maternal toxicity was produced in the rabbit and no embryotoxicity or teratogenicity was observed. There are, however, no adequate and well controlled studies in pregnant women. Like other medicines in its class, ciprofloxacin causes arthropathy in immature animals. Ciprofloxacin should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus (e.g. potential damage to articular cartilage in the immature foetal organism).

Use in lactation
Ciprofloxacin is excreted into human milk. Because of the potential for serious adverse reactions from ciprofloxacin in breastfed infants, a decision should be made to discontinue breastfeeding or to avoid using the medicine, taking into account the importance of the medicine to the mother.

Paediatric use
Ciprofloxacin is not recommended for use in pre-pubertal children. Toxicological studies have shown that ciprofloxacin and related medicines, such as nalidixic acid and cinoxacin, can produce erosions of the cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. The safety and effectiveness of ciprofloxacin in prepubertal children have not been established.

Use in the elderly
Ciprofloxacin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Carcinogenicity
Carcinogenicity studies in mice (oral doses up to 1,090 and 1,455mg/kg/day in males and females, respectively) and rats (241 and 328mg/kg/day in males and females, respectively) showed no evidence of carcinogenicity.

Results from photo-co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV-induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m^2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16-32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

Mutagenicity
Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay *in vitro*, but not in other mammalian systems *in vitro* or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the medicine did not exhibit any cytogenetic effect.

Effect on laboratory tests:
Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium* spp. Culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

Effect on ability to drive or operate machinery
Even when taken as prescribed, this medicine can alter patients' responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the medicine is taken in conjunction with alcohol.

INTERACTIONS WITH OTHER MEDICINES

Medicines known to prolong QT interval
Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics as ciprofloxacin may have an additive effect on the QT interval.

Theophylline:
Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Omeprazole:
Concomitant administration of ciprofloxacin and omeprazole results in a slight reduction of C_{max} and area under the curve (AUC) of ciprofloxacin.

Probenecid:
Coadministration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its area under the curve (AUC), without altering the peak concentration, time to peak and half-life of elimination.

Caffeine:
Quinolones have also been shown to interfere with the metabolism of caffeine. They may reduce the clearance of caffeine and prolong its plasma half-life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Anticoagulants:
Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, such as warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored. 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 normalised ratio) is difficult to assess.

Cyclosporin:
Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly. Therefore, it is

frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Metoclopramide:
Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Oral antidiabetic agents:
Hypoglycaemia has been reported when Ciprofloxacin and oral antidiabetic agents, mainly sulfonylureas (e.g. glibenclamide, glimepride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

Nonsteroidal anti-inflammatory drugs (NSAIDs):
Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain NSAIDs (but not acetylsalicylic acid) can provoke convulsions.

Other xanthine derivatives:
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciprofloxacin is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Ciprofloxacin with phenytoin.

Methotrexate:
Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Tizanidine:
Tizanidine serum concentrations increase with concomitant administration with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (see also CONTRAINDICATIONS).

Duloxetine:
In clinical studies it was demonstrated that concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isoenzyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole:
In a clinical study it was shown that 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 of 60% and 84%, respectively. Although ropinirole treatment was well tolerated, case reports suggest that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration. Ropinirole-related side effects should be monitored during and shortly after co-administration with ciprofloxacin; dose adjustment is recommended if necessary.

Lidocaine:
It was demonstrated in healthy subjects that concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Others:
Iron, sucralfate or highly buffered medicines (e.g. didanosine, an antiretrovirals), polymeric phosphate binders (e.g. sevelamer) and antacids containing magnesium, aluminium or calcium interfere with the absorption of ciprofloxacin. Concurrent administration of these agents with ciprofloxacin should be avoided.

Clozapine:
Following concomitant administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised

Sildenafil:
C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

ADVERSE EFFECTS

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n=51,721; data lock point: 15 May 2005).

Common greater than or equal to 1% to <10%; uncommon greater than or equal to 0.1% to <1%; rare greater than or equal to 0.01% to <0.1%; very rare <0.01%.

Infections and infestations:
Uncommon: candida infections, mycotic superinfections.
Rare: antibiotic associated colitis (very rarely with possible fatal outcome).

Blood and lymphatic system disorders:
Uncommon: eosinophilia.
Rare: leucopenia, anaemia, neutropenia, leucocytosis, thrombocytopenia, thrombocytaemia.
Very rare: haemolytic anaemia, agranulocytosis, pancytopenia (life threatening*), bone marrow depression (life threatening*).

Immune system disorders:
Rare: allergic reaction, allergic oedema/angioedema.
Very rare: anaphylactic reaction, anaphylactic shock (life threatening*), serum sickness-like reaction*.

Metabolism and nutrition disorders:
Uncommon: anorexia.
Rare: hyperglycaemia, hypoglycaemia.

Psychiatric disorders:
Uncommon: psychomotor hyperactivity/ agitation.
Rare: confusion and disorientation, anxiety reaction, abnormal dreams, depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide), hallucinations.
Very rare: psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide).

Nervous system disorders:
Uncommon: headache, dizziness, sleep disorders, taste disorders.
Rare: paraesthesia and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo.
Very rare: migraine, disturbed coordination, smell disorders, hyperaesthesia*, intracranial hypertension (pseudotumour cerebri)*.

Eye disorders:
Rare: visual disturbances.
Very rare: visual colour distortions.

Ear and labyrinth disorders:
Rare: tinnitus, hearing loss.
Very rare: hearing impaired.

Cardiac disorders:
Rare: tachycardia.

Vascular disorders:
Rare: vasodilatation, hypotension, syncope.
Very rare: vasculitis.

Respiratory, thoraric and mediastinal disorders:
Rare: Dyspnoea (including asthmatic condition).

Gastrointestinal disorders:
Common: nausea, diarrhoea.
Uncommon: vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence.
Very rare: pancreatitis.

Hepatobiliary disorders:
Uncommon: transient increase in transaminases, increased bilirubin.
Rare: hepatic impairment, jaundice, hepatitis (noninfective).
Very rare: Liver necrosis (very rarely progressing to life threatening hepatic failure*).

Skin and subcutaneous tissue disorders:
Uncommon: rash, pruritus, urticaria.
Rare: photosensitivity reactions, unspecific blistering.
Very rare: petechiae, erythema multiforme minor, erythema nodosum*, Stevens-Johnson syndrome (potentially life threatening)*, toxic epidermal necrolysis (potentially life threatening)*.

Musculoskeletal, connective tissue and bone disorders:
Uncommon: arthralgia.
Rare: myalgia, arthritis, increased muscle tone and cramping.
Very rare: muscular weakness, tendonitis, 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:
Common: injection and infusion site reactions (only intravenous administration), e.g. phlebitis or thrombophlebitis.
Uncommon: unspecific pain, feeling unwell, fever.
Rare: oedema, sweating (hyperhidrosis).
Very rare: gait disturbance*.

Investigations:
Uncommon: increase in blood alkaline phosphatase.
Rare: prothrombin level abnormal, increased amylase.

Note: The incidence of arthropathy, mentioned above, refers to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

* Adverse reactions derived from post-marketing reports (status: 31 July 2005) for which a frequency could not be estimated are listed below:

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance
Investigations	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see PRECAUTIONS).

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

Common: vomiting, transient increase in transaminases, rash.

Uncommon: thrombocytopenia, thrombocytaemia, confusion and disorientation, hallucinations, paraesthesia and dysaesthesia, seizures, vertigo, visual disturbances, hearing loss, tachycardia, vasodilatation, hypotension, transient hepatic impairment, jaundice, renal failure, oedema.

Rare: pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impairment, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture.

DOSAGE AND ADMINISTRATION

Adults

Urinary tract infections. The usual dosage is 250mg every twelve hours. For patients with complicated infections caused by organisms not highly susceptible such as *Enterococcus faecalis*, 500mg may be administered every twelve hours.

Bronchial infections, skin and skin structure infections. The usual dose is 500mg every twelve hours. For more severe or complicated infections, a dosage of 750mg may be given every twelve hours.

Bone and joint infections. 750mg every twelve hours.

Gastroenteritis (infectious diarrhoea). 500mg every twelve hours.

Acute, uncomplicated gonorrhoeal urethritis. A single 250mg dose.

Chronic bacterial prostatitis. 250 to 500mg every twelve hours.

Note: The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host defence mechanisms and the status of renal function.

Gram-positive organisms are generally less sensitive than Gram-negative organisms, the use of higher doses should be considered in patients with Gram-positive infections. In such cases eight hourly administration of ciprofloxacin 500mg may be preferable.

Duration of treatment

It depends upon the severity of infection. Generally, ciprofloxacin should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days, however for severe and complicated infections more prolonged therapy may be required. Bone and joint infections may require treatment for four to six weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only five days. Chronic bacterial prostatitis should be treated for 14 to 28

days. In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Infants and Children

Ciprofloxacin is not recommended for the use in prepubertal children (See PRECAUTIONS).

Use in the Elderly

Ciprofloxacin should be used with caution (See PRECAUTIONS).

Use in patients with renal impairment

Dosage adjustments for patients with creatinine clearance between 31-60mL/minute/1.73m², the maximum daily dose should be 1,000mg/day for oral administration. For creatinine clearance less than or equal to 30mL/minute/1.73m², the maximum daily dose should be 500 mg/day for oral administration.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance. Please refer to equation 1.

Equation 1
Calculation of creatinine clearance (mL/min)

$$\text{Men: } \frac{\text{Bodyweight (kg)} \times (140 - \text{age in years})}{72 \times \text{serum creatinine (mmol/L)}} \times 0.0885$$

Women: multiplication of the result of the above equation by 0.85.

OVERDOSAGE

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 in some cases.
Apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg- or Ca-containing antacids which reduce the absorption of ciprofloxacin. Patients should be kept well hydrated.

Only a small amount of ciprofloxacin (<10%) is eliminated from the body after 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.

Contact the Poisons Information Centre on 13 11 26 for advice on management of overdose.

PRESENTATION AND STORAGE CONDITIONS

Tablets:

250 mg – round white film-coated tablets, with a breaking notch on one side, embossed with 'cip 250'.Each tablet contains ciprofloxacin hydrochloride equivalent to 250mg ciprofloxacin.

500 mg – oblong white film-coated tablets, with breaking notch on both sides, embossed with 'cip 500'. Each tablet contains ciprofloxacin hydrochloride equivalent to 500mg ciprofloxacin.

750 mg - oblong white film-coated tablets, with breaking notch on both sides, embossed with 'cip 750'. Each tablet contains ciprofloxacin hydrochloride equivalent to 750mg ciprofloxacin.

All three strengths of the tablets; 250 mg, 500 mg, and 750 mg, are available in blisters of 14 tablets.

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
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Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 26/04/2002

Date of most recent amendment: 24/12/2015