AUSTRALIAN PRODUCT INFORMATION

C-FLOX

ciprofloxacin (as hydrochloride) film-coated tablets

1 NAME OF THE MEDICINE

Ciprofloxacin (as hydrochloride)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

C-FLOX film-coated tablets contain either 250 mg, 500 mg or 750 mg of ciprofloxacin (as hydrochloride) as the active ingredient.

Excipients of known effect: Traces of sulfites.

For the full list of excipients, see section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

C-FLOX 250: a white, biconvex, round, film-coated tablet marked "CF" scoreline "250" on one side and "G" on the other, each containing 250 mg of ciprofloxacin.

C-FLOX 500: a white, biconvex, capsule shaped, film-coated tablet marked "CF" scoreline "500" on one side and "G" on the other, each containing 500 mg of ciprofloxacin.

C-FLOX 750: a white, biconvex, capsule shaped, film-coated tablet marked "CF" scoreline "750" on one side and "G" on the other, each containing 750 mg of ciprofloxacin.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

C-FLOX is indicated for the 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
- Inhalational anthrax (post-exposure): to reduce the incidence or progression of disease following exposure to aerosolised *Bacillus anthracis*. Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication

Note:

1. Typhoid and Paratyphoid infections and infections due to multi-resistant *Staphylococcus aureus* are excluded from the above due to insufficient data

2. Because Gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with Gram-positive infections, such as pneumonia due to *Streptococcus pneumoniae*

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

Strains of *Neisseria 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 may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

C-FLOX 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 aetiologic agents, additional therapy should be considered.

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Urinary Tract Infections

The usual adult dosage is 250 mg every 12 hours. For patients with complicated infections caused by organisms not highly susceptible, such as Enterococcus faecalis, 500 mg may be administered every 12 hours.

Bronchial Infections, Skin and Skin Structure Infections

The usual dose is 500 mg every 12 hours. For more severe or complicated infections, a dosage of 750 mg may be given every 12 hours.

Bone and Joint Infections

750 mg every 12 hours.

Gastroenteritis (infectious diarrhoea)

500 mg every 12 hours.

Acute, Uncomplicated Gonorrhoeal Urethritis

250 mg as a single dose.

Chronic Bacterial Prostatitis

250 to 500 mg every 12 hours.

Inhalational Anthrax (post-exposure)

For adults, the recommended dose is 500 mg every 12 hours.

For paediatric patients, the recommended dose is 15 mg/kg per dose (not to exceed 500 mg per dose), every 12 hours.

Drug administration should begin as soon as possible after suspected or confirmed exposure.

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.

Because 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 8 hourly administration of 500 mg ciprofloxacin may be preferable.

Duration

The duration of treatment depends upon the severity of infection. Generally, ciprofloxacin should be continued for at least 2 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 4 to 6 weeks or longer. Gastrointestinal infections (infectious diarrhoea) need treatment for only 5 days. Chronic bacterial prostatitis should be treated for 14 to 28 days.

Inhalational anthrax (post exposure) should be treated for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

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

Missed dose

If a dose is missed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Impaired Renal Function

Dosage adjustments: for patients with creatinine clearance between 31 to 60 mL/min/1.73m^2 – the maximum daily dose should be 1000 mg/day for oral administration. For creatinine clearance equal or less than 30 mL/min/1.73m^2 – 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:

Men: Creatinine clearance (mL/min) = $\dfrac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mmol/L)}}$ x 0.0885

Women: 0.85 x the value calculated for men

4.3 CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin, other quinolones, including nalidixic acid, or any of the excipients.

Concurrent administration of ciprofloxacin and tizanidine (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (see CNS Effects and Psychiatric reactions) and musculoskeletal system (see Tendonitis and tendon rupture).

Streptococcus pneumoniae Infections

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

Cardiac Disorders

Ciprofloxacin is associated with cases of QT prolongation (see section 4.8 Adverse Effects (Undesirable Effects)). 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) (See Section 4.5 Interactions with other medicines and other forms of interactions) or in patients with risk factors for QT prolongation or torsade de pointes (e.g. congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

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 drug discontinuation alone. However, in moderate to severe cases appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated.

Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil™), may prolong and/or worsen the condition and should not be used.

Myasthenia gravis

Ciprofloxacin should be used with caution in patients with myasthenia gravis because symptoms can be exacerbated. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Tendonitis and tendon rupture

Tendonitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, 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, and cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. At any sign of tendonitis (e.g. painful swelling, inflammation), the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued.

Superinfections

As with other broad-spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible 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 Pseudomonas aeruginosa, bacterial eradication is usually not achieved. Resistance to

ciprofloxacin has been shown to develop in a significant proportion of Pseudomonas aeruginosa infections in cystic fibrosis patients following a single course of the drug.

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 such cases, the drug 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.

CNS Effects

As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures.

In some instances, CNS reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin.

Psychiatric reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions including: toxic psychosis, psychotic reactions progressing to suicidal ideations/thoughts, hallucinations or paranoia; depression, or self-injurious behaviour such as attempted or completed suicide; anxiety, agitation or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These reactions may occur following the first dose. Advise patients receiving ciprofloxacin to inform their healthcare provider immediately if these reactions occur, discontinue the drug and institute appropriate care.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness in order to prevent the development of an irreversible condition (see section 4.8 Adverse Effects (Undesirable Effects)).

Vision Disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section 4.8 Adverse Effects (Undesirable Effects)).

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxanthines, caffeine, duloxetine, clozapine, olanzapine, ropinirole, agomelatine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see section 4.5 Interactions with Other Medicines and Other Forms of Interactions).

Dysglycaemia

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with ciprofloxacin. In ciprofloxacin-treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see Section 4.8 Adverse effects (Undesirable effects)).

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 dissection, or in the 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.

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 drug, 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 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.

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 system adverse effects. Cases of status epilepticus have been reported. If seizures occur, ciprofloxacin should be discontinued.

Use in Hepatic Impairment

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 section 4.8 Adverse Effects (Undesirable 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.

Use in Renal Impairment

Alteration of the dosage regimen is necessary for patients with impairment of renal function (see section 4.2 Dose and Method of Administration).

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 (see section 4.2 Dose and Method of Administration).

Paediatric Use

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid and cinoxacin, can produce erosions of 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.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure) (see section 4.2 Dose and Method of Administration).

The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Effects 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drugs Known to Prolong QT Interval

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

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 AUC of ciprofloxacin.

Probenecid

Co-administration of probenecid with ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance and a 50% increase in its AUC, without altering the peak concentration, time to peak and half-life of elimination.

Anticoagulants

Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, 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.

Ciclosporin

Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving ciclosporin 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, glimepiride), where co-administered, presumably by intensifying the action of the oral antidiabetic agent.

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Animal studies have shown that the combination of very high doses of fluoroquinolones (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. Quinolones may reduce the clearance of caffeine and prolong its plasma half-life and therefore may enhance the effects of caffeine.

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.

Chelation complex formation

The simultaneous administration of ciprofloxacin and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. antiretrovirals) 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.

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 section 4.3 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 moderate 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 (lignocaine)

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

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. 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. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase in agomelatine exposure. Although no clinical data are available, ciprofloxacin is a moderate inhibitor of CYP450 1A2 and similar effect can be expected upon concomitant administration. Therefore, concurrent use of ciprofloxacin with agomelatine is not recommended (see section 4.4 Special Warnings and Precautions for Use – Cytochrome P450).

Zolpidem

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data available.

Use in Pregnancy

Pregnancy Category: B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/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, intra-uterine deaths and fetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/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 drugs 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 fetus (e.g. potential damage to articular cartilage in the immature fetal organism).

Use in Lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Even when taken as prescribed, this drug can alter a patient's responsiveness, impairing the ability to drive or operate machinery. This is even more applicable when the drug is taken in conjunction with alcohol.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience

Table 1 - 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 = 51721, data lock point: 15 May 2005).

Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%	Very rare < 0.01%
Infections and Infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
Blood and Lymphatic System Disorders			
	Eosinophilia	Leukopaenia Anaemia Neutropaenia Leukocytosis Thrombocytopaenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopaenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders			
		Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia	
Psychiatric Disorders			
	Psychomotor hyper-activity/agitation	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	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			

Common **≥ 1% to < 10%**	**Uncommon** **≥ 0.1% to < 1%**	**Rare** **≥ 0.01% to < 0.1%**	**Very rare** **< 0.01%**
		Visual disturbances	Visual colour distortions
Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic conditions)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non-infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis 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			
Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombin levels Increased amylase	

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

Post-marketing Experience

Table 2 - ADRs 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	Pancytopaenia (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) Drug reaction with eosinophilia and systemic symptoms (DRESS) (potentially life-threatening)
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 section 4.4 Special Warnings and Precautions for Use).

In isolated instances, some serious adverse drug reactions may be long-lasting (>30 days) and disabling; such as tendonitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

Table 3 - 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, Par- 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 impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including

urinary pH and acidify if required to prevent crystalluria. Patients should be kept well hydrated - calcium or magnesium-containing antacids reduce the absorption of ciprofloxacin in overdoses.

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action (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 species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis; Proteus vulgaris; Providencia stuartii; Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species* (including *Serratia marcescens*); *Pseudomonas aeruginosa; Pseudomonas fluorescens; Campylobacter* species; *Haemophilus influenzae; Moraxella (Branhamella) catarrhalis*.

Gram-Positive*

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

*Note:

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

2. Most strains of *Streptococci* are only moderately susceptible to ciprofloxacin. Clinical studies have shown ciprofloxacin 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 *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract

3. 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*

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

5. 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 (see section 5.2 Pharmacokinetic Properties – Inhalational Anthrax).

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 2 to 8 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 Pseudomonas aeruginosa infections, especially in patients with cystic fibrosis, and in Staphylococcus aureus infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms that are resistant to other quinolone agents (e.g. nalidixic acid, cinoxacin, etc.) 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 the results of these tests are known; once results become available, appropriate therapy should be continued.

Disc Susceptibility Test

Dilution or infusion techniques – either quantitative (MIC) or breakpoint, should be used following a regularly, updated recognised and standardised method (e.g. 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 drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug 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. Local information on resistance is desirable, particularly when treating severe infections.

Clinical Trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

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 below:

Ciprofloxacin – Serum concentrations after oral dosing

Dose (mg)	Maximum Serum Concentration (µg/mL)	Area Under Curve (AUC) (µg.hr/mL)
250	1.4	5.4
500	2.6	10.6
750	3.4	15.0

Maximum serum concentrations are attained 1 to 2 hours after oral dosing. Mean concentrations 12 hours after dosing with 250, 500 or 750 mg are 0.1, 0.2 and 0.4 µg/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.

Excretion

The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. During the first 2 hours after an oral dose of 250 mg, the urine concentration of ciprofloxacin usually exceeds 200 µg/mL. Eight to 12 hours after the same dose, urine levels are approximately 30 µg/mL. Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/h which exceeds the normal glomerular filtration rate of 7.2 L/h. Thus, active tubular secretion would seem to play a significant role in its elimination. In patients with creatinine clearance between 21 to 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 (creatinine clearance less than 20 mL/min), the half-life of ciprofloxacin is nearly doubled, and dosage adjustment is necessary (see section 4.2 Dose and Method of Administration).

Although bile concentrations of ciprofloxacin are 3 to 4 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 5 days after dosing.

Inhalational Anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see section 4.2 Dose and Method of Administration). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 µg/mL, and 4.56 µg/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 µg/mL.

In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 µg/mL and trough concentrations range from 0.09 to 0.26 µg/mL, following two 30-minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 µg/mL after the initial oral dose. Long-term safety data, including effects on cartilage, following the administration of ciprofloxacin

to paediatric patients are limited (see section 4.4 Special Warnings and Precautions for Use - Paediatric Use). Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10^5) spores (range 5 to 30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/mL. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p = 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the highest recommended human dose of 1500 mg/day based upon body surface area) 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/m2), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16 to 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 tumours. 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 drug did not exhibit any cytogenetic effect.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following excipients: microcrystalline cellulose, maize starch, crospovidone, pregelatinised maize starch, colloidal anhydrous silica, magnesium stearate, hypromellose, titanium dioxide, polydextrose, triacetin and macrogol 8000.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25ºC.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type: blister pack (PVC/PVDC/Al)

Pack sizes: 2 (250 mg only), 14 tablets

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

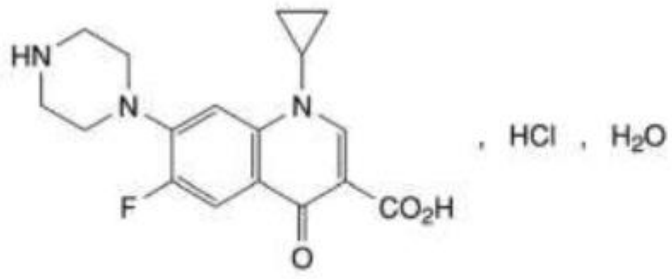
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Structure

Ciprofloxacin hydrochloride is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity. It is the monohydrochloride monohydrate salt of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid.

Ciprofloxacin hydrochloride 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.



Chemical name: 1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-quinoline-3-carboxylic acid hydrochloride

Molecular formula: $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$

Molecular weight: 385.8

CAS Number

86393-32-0

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd

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Millers Point NSW 2000

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9 DATE OF FIRST APPROVAL

19/04/2012

10 DATE OF REVISION

04/08/2022

Summary Table of Changes

Section Changed	Summary of New Information
4.8	Update to post marketing experience to include DRESS.

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