NEW ZEALAND DATA SHEET

Ipca-Ciprofloxacin

1. PRODUCT NAME

Ipca-Ciprofloxacin 250 mg, 500mg, 750 mg, film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Film-coated tablets

Ciprofloxacin 250:
1 tablet contains ciprofloxacin hydrochloride equivalent to 250 mg ciprofloxacin.

Ciprofloxacin 500:
1 tablet contains ciprofloxacin hydrochloride equivalent to 500 mg ciprofloxacin.

Ciprofloxacin 750:
1 tablet contains ciprofloxacin hydrochloride equivalent to 750 mg ciprofloxacin.

3. PHARMACEUTICAL FORM

Film-coated tablet:
250 mg:
White to creamish-white, round, biconvex film coated tablets with CPR 250 embossed on one side and 'BL' on the other.

500 mg:
White to creamish-white caplet shaped film coated tablets with CPR 500 embossed and with scoreline on one side and 'BL' on the other.

750 mg:
White to creamish-white capsule shaped film coated tablets with CPR 750 embossed on one side and 'BL' on the other.

Do not halve the tablet. Dose equivalence when the tablet is divided has not been established.

4. CLINICALPARTICULARS

4.1 Therapeutic indications

Ciprofloxacin is indicated for the treatment of bacterial infections caused by susceptible organisms. Ciprofloxacin should only be prescribed when other antibiotics commonly recommended for the infection are inappropriate.

Adults

- Lower respiratory tract infections including pneumonia
- Renal and/or genitourinary tract infections including adnexitis, gonorrhea, prostatitis
- Gastrointestinal and/or biliary tract infections including peritonitis
- Skin and soft tissue infections
- Bone and joint infections
- Sepsis
- Inhalational anthrax (post-exposure): to reduce the incidence of progression of disease following exposure to aerosolized *Bacillus anthracis*.

Children

Cystic fibrosis

For the treatment of acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients aged 5-17 years.

Inhalational anthrax (post-exposure)
For the indication of inhalational anthrax (post-exposure).

Complicated urinary tract infections and pyelonephritis
For complicated urinary tract infections or pyelonephritis due to *E.coli* in paediatric patients aged 1-17 years.

The risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints/surrounding tissues. The use of ciprofloxacin for other indications is not recommended in children.

4.2 Dose and method of administration

Adults

Unless otherwise prescribed, the following guideline doses are recommended:

Infection	Dose and therapy duration
Respiratory tract infections Urinary tract infections	250-500mg twice daily Usual duration of treatment: 7-14 days
Gastrointestinal infections Skin and soft tissue infections Prostatitis Inhalational anthrax	500mg twice daily Usual duration of treatment: 3-7 days (gastrointestinal infections) 5-10 days (skin and soft tissue infections) Up to 28 days (prostatitis) 60 days (inhalational anthrax)
Gonorrhoea	250mg as a single dose
Severe systemic infections eg bone and joint infections, peritonitis, sepsis	750mg twice daily Usual duration of treatment: 7-14 days maximum of 2 months in osteomyelitis

*Consideration should be given to local guidelines on the appropriate use of antibacterial agents

Ipca-Ciprofloxacin

Elderly

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

Children

Cystic Fibrosis (acute pulmonary exacerbation associated with *P. aeruginosa*)

The recommended oral dose is20 mg/kg twice daily (maximum daily dose 1500 mg) for 10-14 days.

Inhalational anthrax (post-exposure)

The recommended oral dose is 15 mg/kg twice daily (maximum dose of 500 mg per dose, 1000 mg per day) for 60 days. Drug administration should begin as soon as possible after suspected or confirmed exposure.

Complicated urinary tract infections and pyelonephritis

The recommended oral dose is 10 to 20 mg/kg every 12 hours with a maximum of 750 mg per dose for 10-21 days.

Method of Administration:

The tablets are swallowed whole with a small amount of fluid. Do not halve tablet.

Dose equivalence when the tablet is divided has not been established.

Tablets can be taken independent of mealtimes. (If the tablets are taken on an empty stomach, the active substance is absorbed more rapidly). In this case, tablets should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice). However, dietary calcium as part of a meal does not significantly affect ciprofloxacin absorption.

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Renal & Hepatic impairment:

Adults

1. I

Impaired renal and hepatic function (recommendations apply to adults only):

Creatinine clearance	Serum creatinine	Dose
31-60 mL/min/1.73m^2	120-170 µmol (1.4 to 1.9 mg/dL)	Maximum dose 1000 mg/day
≤ 30 mL/min/1.73m^2	≥175 µmol (≥ 2.0 mg/dL)	Maximum dose 500 mg/day*

2.

Impaired renal function + haemodialysis

Recommended dose: 500mg per day administered as a single dose following haemodialysis

Impaired renal function + continuous ambulatory peritoneal dialysis (CAPD)

Recommended dose: 500mg per day administered as a single dose following CAPD

Impaired hepatic function

Dose adjustment is not necessary in mild to moderate hepatic failure but may be considered necessary in severe hepatic failure.

Children and adolescents (5-17 years):

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

Children

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

4.3 Contraindications

Ciprofloxacin must not be used in cases of hypersensitivity to ciprofloxacin or other quinolone chemotherapeutics or any of the excipients.

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.

4.4 Special warnings and precautions for use

Prolonged, disabling, and potentially irreversible/persistent serious adverse drug reactions:Fluoroquinolones including ciprofloxacin have been associated with cases of prolonged (continuing for months or years), disabling and potentially persistent/irreversible serious adverse reactions affecting different, sometimes multiple body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **4.8 Undesirable effects**). In general, elderly patients may be more susceptible to medicine 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 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).

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.Children and adolescents

As with medicinal products in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. The analysis of available safety data from ciprofloxacin use in patients less than 18 years of age, the majority of whom had cystic fibrosis, did not disclose any evidence of medicine related cartilage or articular damage. The use of ciprofloxacin for indications other than the treatment of acute pulmonary exacerbation of cystic fibrosis caused by *P. aeruginosa* infection (children aged 5-17 years), complicated urinary tract infections and pyelonephritis due to *E.coli* (children aged 1-17 years) and for the use in inhalational anthrax (post-exposure) was not studied. For other indications clinical experience is 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
"Inhalational Anthrax – Additional Information in Pharmacodynamic Properties".

Hypersensitivity:

In some instances, the hypersensitivity and allergic reactions occurred after the first administration. The doctor should be informed immediately.

Anaphylactic/anaphylactoid reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases ciprofloxacin has to be discontinued, medical treatment (e.g. treatment for shock) is required.

Musculoskeletal system/effect on tendons:

Tendonitis and other tendon ruptures (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 or up to several months after discontinuation of ciprofloxacin.

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. Therapy should be discontinued if the patient experiences any signs of tendonitis (e.g. painful swelling, inflammation) or rupture of a tendon. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise, a physician should be consulted, and the antibiotic treatment should be discontinued due to the increased risk of tendon rupture.

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, may prolong and/or worsen the condition and should not be used.

Hepatic disorders

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 Undesirable effects) There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

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. Ciprofloxacin should be used with caution in patients with CNS disorders, such as severe cerebral arteriosclerosis or epilepsy. 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, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see Section 4.8 Undesirable effects)

Seizures:
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.

Skin and Appendages:
Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i. e. sunburn-like skin reactions) occurs.

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 Undesirable effects)

Myasthenia gravis
Ciprofloxacin should be used with caution in patients with myasthenia gravis because.
symptoms can be exacerbated (see Section 4.8 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 Undesirable effects)

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

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 nonvegetarians 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.

Severe infections and/or infections due to Gram-positive or anaerobic bacteria
For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, ciprofloxacin should be used in combination with an appropriate antibacterial agent.

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

Genital tract infections
Genital tract infections may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. In genital tract infections thought or known to be due to *N. gonorrhoeae*, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

Cytochrome P450:
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicinal products are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. theophylline, methylxantines, caffeine, duloxetine, clozapine).

Increased plasma concentrations associated with medicine specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin. **(**See **4.5 Interaction with other medicinal products and other forms of interaction).**

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4.5 Interaction with other medicines and other forms of interaction

Interaction with 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.

Interaction with other medicinal products and other forms of interaction

Class IA or III antiarrhythmics

Precaution should be taken when using ciprofloxacin together with class IA or III antiarrhythmics as ciprofloxacin may have an additive effect on the QT interval.

Chelation Complex Formualtion

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 medicines (e.g. didanosine tabelts), 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.

This restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

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

Omeprazole

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

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline induced side effects; in very rare cases these side effects can be life-threatening or fatal. If concurrent use of the two products is unavoidable, the serum theophylline concentration should therefore be checked and the theophylline dose appropriately reduced.

Other xanthine derivatives

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

NSAID

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

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

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

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

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.

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.

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.

Tizanidine
In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect.
Tizanidine must not be administered together with ciprofloxacin (see **4.3 Contraindications**).

Duloxetine
In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme 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. Monitoring ropinirole-related side effects dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

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.

Clozapine
Following concomitant and administration of 250 mg ciprofloxacin for 7 days, serum concentration 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 two-fold 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.

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.

4.6 Fertility, pregnancy and lactation

Pregnancy
Since the safety of ciprofloxacin in pregnant women has not been established and since, on the basis of animal studies, it is not entirely improbable that the medicine could cause damage to articular cartilage in the immature foetal organism (see **5.3 Preclinical Safety Data**), ciprofloxacin must not be prescribed to pregnant women.

Animal studies have not shown any evidence of teratogenic effects (malformations).

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding (see **5.3 Preclinical Safety Data**).

4.7 Effects on ability to drive and use machines
Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions. This applies particularly in combination with alcohol.

4.8 Undesirable effects

Adverse Reactions based on all clinical studies with ciprofloxacin sorted by CIOMS III categories of frequency are listed below (n = 51721 patients, data lock point: 15 May 2005).

The frequencies of Adverse Drug Reactions (ADRs) reported with ciprofloxacin are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1000 to <1/100)
Rare (≥1/10000 to <1/1000)
Very rare (<1/10000)
Not known (cannot be estimated from the available data)

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The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and Infestations		Mycotic superinfections Candida infections	Antibiotic associated colitis (very rarely with possible fatal outcome)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytsosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic oedema/ angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia Decreased appetite and food intake	Hyperglycaemia Hypoglycemia		
Psychiatric Disorders		Psychomotor hyperactivity/ agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (possibly culminating in self-injurious behavior such as suicidal ideation/thoughts and completed suicide) Hallucinations	Psychotic reactions (possibly culminating in self-injurious behavior such as suicidal ideation/ thoughts and completed suicide)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures(including status epilepticus)Vertigo	Migraine Disturbed co-ordination Smell disorders Hyperesthesia Intracranial Hypertension (pseudotumour cerebri)	Peripheral neuropathy and polyneuropathy
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss	Hearing impaired	

Cardiac Disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de pointes*
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dysponea (including Asthmatic condition)		

Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary 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 Pruritis Urticaria	Photosensitvity reactions Unspecific blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalized exanthematous pustulosis (AGEP) Drug reaction with eosinophilia and systemic symptoms (DRESS) (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 Administrations Site Disorders		Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

* These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see 4.4 **Special Warnings and Precautions for Use**). Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including

reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia and neuralgia, fatigue, psychiatric symptoms (including sleep disorders, anxiety, panic attacks, depression and suicidal ideation), memory and concentration impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4).

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 of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions
https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose
In the event of acute, excessive oral over dosage, reversible renal toxicity has been reported in some cases.
Therefore, 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.

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

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICALPROPERTIES
5.1 Pharmacodynamic properties
Ciprofloxacin is a synthetic broad spectrum antibacterial agent (ATCCODE: J 01 MA 02).

Mechanism of Action
Ciprofloxacin is effective *in vitro* against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of bacterial type II topoisomerases (DNA gyrase and topoisomerase IV), which are required for bacterial DNA replication, transcription, repair, and recombination.

Mechanism of Resistance
In vitro resistance to ciprofloxacin is commonly due to mutations in bacterial topoisomerases and DNA gyrase through multiple-step mutations. Single mutations may result in reduced susceptibility rather than clinical resistance, but multiple mutations generally result in clinical resistance to ciprofloxacin and cross-resistance across the quinolone class.

Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by the *qnr* gene has been reported.

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Resistance mechanisms that inactive penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines may not interfere with the antibacterial activity of ciprofloxacin and there is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. Organisms resistant to these medicines may be susceptible to ciprofloxacin.

The minimum bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

In vitro Susceptibility to Ciprofloxacin

The prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought where the local prevalence of resistance is such that utility of the agent, in at lease some types of infections, is questionable.

The bacterial genus and species listed below have been shown to commonly be susceptible to ciprofloxacin *in vitro*:

Aerobic Gram-Positive Microorganisms
Bacillus anthracis
Staphylococcus aureus (methicillin-susceptible)
Staphylococcus saprophyticus
Streptococcus spp.

Aerobic Gram-Negative Microorganisms:

Aeromonas spp.	*Moraxella catarrhalis*
Brucella spp.	*Neisseria meningitidis*
Citrobacter koseri	*Pasteurella* spp.
Francisella tularensis	*Salmonella* spp.
Haemophilus ducreyi	*Shigella* spp.
Haemophilius influenzae	*Vibrio* spp.
Legionella spp.	*Yersinia pestis*

Anaerobicmicroorganisms
Mobiluncus

Other Microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

The following microorganisms show varying degrees of susceptibility to ciprofloxacin:
Acinetobacter baumann, *Burkholderia cepacia*, *Campylobacter* spp., *Citrobacterfreudii, Enterococcus faecalis*, *Enterobacter aerogenes*, En*terobacter clocae, Escherichia coli, Klebsiella pneumoniae, Klebsiella oxytoca, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia* spp*., Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens, Streptococcus pneumoniae, Peptostreptococcus* spp*., Propionibacterium acnes.*

The following microorganisms are considered inherently resistant to ciprofloxacin:
Staphylococcus aureus (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces*, *Enteroccus faecium*, *Listeria monocytogenes*, *Mycoplasma genitalium*, *Ureaplasma urealitycum*, anaerobic microorganisms (Except *Mobiluncus, Peptostreptococus*, *Propionibacterium acnes*).

Inhalational anthrax – additional information
Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition, avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose.

The recommended use in human subjects is based primarily on *in vitro* susceptibility and on animal experimental data together with limited human data. Two month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician is referred to national and /or international consensus documents regarding treatment of 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 regimens (see **4.2 Dosage And Method Of Administration).**

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 5-30 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 medicine administration period.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin film coated tablets, ciprofloxacin is absorbed rapidly and extensively mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

	Mean Ciprofloxacin Serum Concentrations (mg/L) after Oral Administration (Time from tablet intake)		
Time (h)	**250mg**	**500mg**	**750mg**
0.5	0.9	1.7	2.9
1.0	1.3	2.5	3.5
2.0	0.9	2.0	2.9
4.0	0.5	1.7	1.7
8.0	0.3	0.6	0.8
12.0	0.2	0.4	0.5

The absolute bioavailability is approximately 70-80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

Distribution
The protein binding of ciprofloxacin is low (20-30%), and the substance is present in plasma largely in a non-ionised form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state volume of distribution of 2-3 L/kg body weight shows that ciprofloxacin penetrates into tissues resulting in concentrations which clearly exceed the corresponding serum levels.

Metabolism
Small concentrations of 4 metabolites have been reported. They were identified as desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 display antibacterial activity comparable to or inferior to that of nalidixic acid. M 4, with the smallest quantity, is largely equivalent to norfloxacin in its antimicrobial activity.

Excretion
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, non-renally.

Excretion of Ciprofloxacin (% of dose) Oral Administration		
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 0.18-0.3 L/h/kg and the total body clearance between 0.48-0.60 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion.

Non-renal clearance of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolisation. 1% of the dose is via the biliary excreted route. Ciprofloxacin is present in the bile in high concentrations.

Children
In a study in children, C_{max} and AUC were not age-dependent. No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg/TID) was observed.

5.3 Preclinical safety data
The acute toxicity of ciprofloxacin after oral administration can be classified as very low.

Species	**LD_{50} (mg/kg)**
Mouse	Approx. 5000
Rat	Approx. 5000
Rabbit	Approx. 2500

Chronic Toxicity
Subacute tolerability studies over 4 weeks:
Doses up to and including 100 mg/kg were tolerated without damage by rats.
Pseudoallergic reactions due to histamine release were observed in dogs.

Subchronic Toxicity Studies over 3 months
All doses up to and including 500 mg/kg were tolerated without damage by rats. In monkeys, crystalluria and changes in the renal tubules were observed in the highest-dose group (135 mg/kg).

Chronic tolerability studies over 6 months
Doses up to and including 500 mg/kg and 30 mg/kg were tolerated without damage by rats and monkeys, respectively. Changes in the distal renal tubules were again observed in some monkeys in the highest-dose group (90 mg/kg).

Carcinogenicity
In carcinogenicity studies in mice (21 months) and rats (24 months) with doses up to approx. 1000 mg/kg bw/day in mice and 125 mg/kg bw/day in rats (increased to 250 mg/kg bw/day after 22 weeks), there was no evidence of a carcinogenic potential at any dose level.

Reproduction toxicology
Fertility studies in rats
Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.

Embryotoxicity studies
These yielded no evidence of any embryotoxic or teratogenic action of ciprofloxacin.

Perinatal and postnatal development in rats
No effects on the perinatal or postnatal development of the animals were detected. At the end of the rearing period histological investigations did not bring to light any sign of articular damage in the young.

Mutagenicity
Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin.
Test results are listed below:

- *Salmonella*: Microsome Test (Negative)
- *E. coli*: DNA Repair Assay (Negative),
- Mouse Lymphoma Cell Forward Mutation Assay (Positive)
- Chinese Hamster V79 Cell HGPRT Test (Negative),
- Syrian Hamster Embryo Cell Transformation Assay (Negative)
- *Saccharomyces cerev.*: Point Mutation Assay (Negative), Mitotic Crossover and Gene Conversion Assay (Negative)
- Rat Hepatocyte Primary Culture DNA Repair Assay (UDS) (Positive)

Thus, two of the eight tests were positive, but results of the following four *in vivo* test systems gave negative results:

- Rat Hepatocyte DNA Repair Assay
- Micronucleus Test (Mice)
- Dominant Lethal Test (Mice)
- Chinese Hamster Bone Marrow

Although two of the eight *in vitro* assays (i.e. the Mouse Lymphoma Cell Forward Mutation Assay and the Rat Hepatocyte Primary Culture DNA Repair Assay [UDS]) were positive, all of the *in vivo* test systems covering all relevant endpoints gave negative results.

In summary, ciprofloxacin poses no significant mutagenic potential. This assessment is confirmed by the negative outcome of the long-term carcinogenicity studies in mice and rats.

Special tolerability studies
It is known from comparative studies in animals, both with the older gyrase inhibitors (e.g. nalidixic and pipemidic acid) and the more recent ones (e.g. norfloxacin and ofloxacin), that this substance class produces a characteristic damage pattern.
Kidney damage, cartilage damage in weight-bearing joints of immature animals, and eye damage may be encountered.

Renal tolerability
The crystallisation observed in the animal studies occurred preferentially under pH conditions that do not apply in man.

The precipitation of crystals in renal tubules does not immediately and automatically lead to kidney damage. In the animal studies damage occurred only after high doses, with correspondingly high levels of crystalluria. For example, although they always caused crystalluria, even high doses were tolerated over 6 months without damage and without foreign-body reactions occurring in individual distal renal tubules.

Damage to the kidneys without the presence of crystalluria has not been observed.
The renal damage observed in animal studies must not, therefore, as is the case e.g. with the aminoglycosides, be regarded as a primary toxic action of ciprofloxacin on the kidney tissue, but as typical secondary inflammatory foreign-body reactions due to the precipitation of a crystalline complex of ciprofloxacin, magnesium, and protein.

Articular tolerability studies
As with other gyrase inhibitors, ciprofloxacin causes damage to the large, weight-bearing joints in immature animals.

The extent of the cartilage damage varies according to age, species, and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs ciprofloxacin at high doses (1.3 to 3.5 times the therapeutic dose) caused articular changes after two weeks of treatment, which were still observed after 5 months. At therapeutic doses, no effects were observed.

Studies aimed at excluding cataractogenic effects
On the basis of the investigations it may be stated from a toxicological point of view that ciprofloxacin treatment does not involve any risk of cataract induction, particularly because in parental administration maximal bioavailability can be assumed and the duration of administration was 6 months.

Retina tolerability studies
Ciprofloxacin binds to the melanin containing structures including the retina. Potential effects of ciprofloxacin on the retina were assessed in various pigmented animal species. Ciprofloxacin treatment had no effect on the morphological structures of the retina and on electroretinographic findings.

Ipca-Ciprofloxacin

6. PHARMACEUTICALPARTICULARS

6.1 List of excipients

Microcrystalline cellulose, maize starch, magnesium stearate, colloidal anhydrous silica, sodium starch glycolate type A (potato starch), hypromellose, purified talc, titanium dioxide (E171), polyethylene glycol.

6.2 Incompatibilities

Not known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container

Blister packs containing 7, 10, 14, 20, 28, 56 or 100 tablets (Not all pack sizes may be available).

6.6 Special precautions for disposal

No special requirements.

7. MEDICINE SCHEDULE

Prescription medicine

8. SPONSOR

Ipca Pharma (NZ) Pty Limited
P O Box 74509
Auckland 1546
+64 21 339188

9. DATE OF FIRST APPROVAL

30.11.2006

10. DATE OF REVISION OF THE TEXT

29.05.2025

SUMMARY TABLE OF CHANGES

Date	Summary of Changes
27.2.2018 9.4.2018	Updated to the SPC style format. Updated to include warning statement regarding fluoroquinolones and the risk of disabling and persistent musculoskeletal and nervous system adverse reactions.
02.03.2023	Product name and sponsor change
19.05.2023	Section 1, 3 and 8 updated
29.05.2025	Updated in line with Med safe recommendations as per AU reference product and MHRA reference product.