NEW ZEALAND DATA

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 debossed on one side and 'BL' on the other.

500 mg:
White to creamish-white caplet shaped film coated tablets with CPR 500 debossed 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 debossed 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. CLINICAL PARTICULARS

4.1 Therapeutic indications Adults

Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens:

Infections of the lower respiratory tract.

In the treatment of outpatients with pneumonia due to Pneumococcus, ciprofloxacin should not be used as a medicine of first choice. Ciprofloxacin can be regarded as a suitable treatment for pneumonias caused by *Klebsiella*, *Enterobacter*, *Proteus*, *E.coli, Pseudomonas, Haemophilus, Branhamella, Legionella, and Staphylococcus*.

Infections of the kidneys and/or the efferent urinary tract.

Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis.

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Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis).

Infections of the skin and soft tissue.

Infections of the bones and joints.

Sepsis.

Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *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.

According to *in vitro* investigations, the following pathogens can be regarded as sensitive:

E. coli, Shigella, Salmonella, Citrobacter, Klebsiella, Enterobacter, Serratia, Hafnia, Edwardsiella, Proteus (indole-positive and indole-negative), *Providencia, Morganella, Yersinia; Vibrio, Aeromonas, Plesiomonas, Pasteurella, Haemophilus, Campylobacter, Pseudomonas, Legionella, Moraxella, Acinetobacter, Brucella, Staphylococcus, Listeria, Corynebacterium, Chlamydia.*

The following show varying degrees of sensitivity:

Neisseria, Gardnerella, Flavobacterium, Alcaligenes, Streptococcus agalactiae, Enterococcus faecalis, Streptococcus pyogenes, Streptococcus pneumoniae, Viridans group Streptococci, Mycoplasma hominis, Mycobacterium tuberculosis, and Mycobacterium fortuitum.

The following are usually resistant:

Enterococcus faecium, Ureaplasma urealyticum, Nocardia asteroides. With a few exceptions anaerobes are moderately sensitive e.g. *Peptococcus,Peptostreptococcus* to resistant e.g.
Bacteroides.

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

Ciprofloxacin is ineffective against *Treponema pallidum*.

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.

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.

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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:

	Recommended Dosage
Respiratory tract infection (according to severity and	2 x 250-500 mg
Urinary tract infections: - acute, uncomplicated - cystitis in women (before menopause) - complicated	1-2 x 250 mg single dose 250 mg 2 x 250-500
Gonorrhoea - extragenital - acute, uncomplicated	1 x 250 mg single dose 250 mg
Diarrhoea	1-2 x 500 mg
Other infections (see Indications)	2 x 500 mg
-Particularly severe, life-threatening infections, i.e. *Streptococcal pneumonia* -Recurrent infections in cystic fibrosis -Bone and joint infections -Septicaemia -Peritonitis In particular when *Pseudomonas, Staphylococcus* or *Streptococcus* is present	2 x 750 mg
Inhalational anthrax (post-exposure) Drug administration should begin as soon as possible after suspected or confirmed	2 x 500 mg

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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
Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (aged 5 -17 years) with acute pulmonary exacerbation associated with *P. aeruginosa* infection, at a dose of 20 mg/kg orally twice daily (maximum daily dose 1500 mg).

Inhalational anthrax (post-exposure)
For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that treatment of paediatric patients with ciprofloxacin is appropriate. For paediatric patients, the recommended oral dose is 15 mg/kg twice daily (not to exceed a maximum dose of 500 mg per dose, 1000 mg per day). Drug administration should begin as soon as possible after suspected or
confirmed exposure.

Complicated urinary tract infections and pyelonephritis
For the indication of complicated urinary tract infections and pyelonephritis, the recommended dose is 10 to 20 mg/kg orally every 12 hours with a maximum of 750 mg per dose.

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.

If the patient is unable to take tablets, because of the severity of the illness or for other reasons, it is recommended to commence the therapy with an intravenous form of ciprofloxacin.
After intravenous administration the treatment can be continued orally.

Duration of Treatment:
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms. Mean duration of treatment:

- 1 day for acute uncomplicated gonorrhoea and cystitis,
- up to 7 days for infections of the kidneys, urinary tract, and abdominal cavity,
- a maximum of 2 months in osteomyelitis,
- 60 days in inhalational anthrax (post-exposure),
- and 7-14 days in all other infections.

In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.
Infections caused by *Chlamydia* should also be treated for a minimum of 10 days.

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Children

Cystic Fibrosis
For acute pulmonary exacerbation of cystic fibrosis associated with P. aeruginosa infection in paediatric patients (aged 5-17 years), the duration of treatment is 10-14 days.

Inhalation anthrax (post-exposure)
For inhalational anthrax (post-exposure), the duration of treatment is 60 days.

Complicated urinary tract infections and pyelonephritis
For complicated urinary tract infections or pyelonephritis due to *E. coli*, the duration of treatment is 10-21 days.

Renal & Hepatic impairment:

Adults

1. Impaired renal function:

1.1 Where creatinine clearance is between 30 and 60 mL/min/1.73m² or where the serum creatinine concentration is between 1.4 and 1.9 mg/100 mL the maximum daily dose should be 1000 mg per day.

1.2 Where creatinine clearance is equal or is less than 30 mL/min/1.73m² or where the serum creatinine concentration is equal or higher than 2.0 mg/100 mL the maximum daily dose should be 500 mg per day.

2. Impaired renal function + haemodialysis:
Dose as in point 1.2; on dialysis days after dialysis.

3. Impaired renal function + continuous ambulatory peritoneal dialysis (CAPD) Administration of ciprofloxacin film coated tablets (oral) as 1 x 500 mg film coated tablet (or 2 x 250 mg film coated tablets).

4. Impaired liver function
No dose adjustment is required.

5. Impaired renal and liver function
Dose adjustment as in points 1.1 and 1.2 above.

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

Fluoroquinolones have been associated with disabling and potentially persistent adverse reactions which to date include, but are not limited to: tendonitis, tendon rupture, peripheral neuropathy and neuropsychiatric effects. See Nervous system and Musculoskeletal system section 4.4 Special warnings and precautions for use.

May cause tendinitis, hypoglycaemia.

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.

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.
Precaution should be taken when using ciprofloxacin with concomitant medicines that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

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.

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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.

Gastrointestinal System:
In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted, since this symptom can hide a serious intestinal disease (life-threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases Ciprofloxacin must be discontinued and appropriate therapy initiated (e. g. vancomycin, orally, 4 x 250 mg/day). Medicines that inhibit peristalsis are contraindicated.

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

Musculo-Skeletal System:
At any sign of tendinitis (e.g. painful swelling, inflammation), a physician should be consulted and the antibiotic treatment be discontinued. Care should be taken to keep the affected extremity at rest and avoid any inappropriate physical exercise due to increased risk of tendon rupture.

Tendon rupture (predominantly Achilles tendon) has been reported predominantly in the elderly on prior systemic treatment with glucocorticoids.

Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment.

Nervous System:
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 at risk because of possible central-nervous side effects.

In some instances the CNS reactions occurred after the first administration of ciprofloxacin. In rare cases depression or psychosis can progress to self-endangering behaviour. In these cases ciprofloxacin has to be discontinued and the doctor should be informed immediately.

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.

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.

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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).

Glibenclamide
In particular cases, concurrent administration of ciprofloxacin and glibenclamide can intensify the action of glibenclamide (hypoglycaemia).

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.

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.

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)

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

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System Organ	Common	Uncommon	Rare	Very Rare	Not Known
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression	
Immune System Disorders			Allergic reaction Allergic oedema/ angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening)	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity/ agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression	Psychotic reactions	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures Vertigo	Migraine Disturbed co-ordination Smell disorders Hyperesthesia Intracranial	Peripheral neuropathy and polyneuropathy
Eye Disorders			Visual disturbance	Visual colour	
Ear and Labyrinth			Tinnitus Hearing loss	Hearing impaired	
Cardiac Disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de pointes*
Vascular Disorder			Vasodilatation Hypotension	Vasculitis	
Respiratory, Thoracic and			Dyspnea (includin		

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Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsi		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non-	Liver necrosis (very rarely progressing to life-threatening hepatic	
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	
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	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administratio		Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatas	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**).

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
Rare	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impaired, vasculitis, pancreatitis, liver necrosis,

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://nzphvc.otago.ac.nz/reporting/

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

5. PHARMACOLOGICAL PROPERTIES
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*

Anaerobic microorganisms
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.*

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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.

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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.

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6. PHARMACEUTICAL PARTICULARS

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
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Auckland 1546
+64 21 339188

9. DATE OF FIRST APPROVAL

30.11.2006

10. DATE OF REVISION OF THE TEXT

12.09.2024

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
02.03.2023	Product name and sponsor change
19.05.2023	Section 1, 3 and 8 updated
12.09.2024	Appearance updated