NEW ZEALAND DATA SHEET

1. CIPROXIN®

Ciproxin 250 mg, film-coated tablets*

Ciproxin 500 mg, film-coated tablets*

Ciproxin 750 mg, film-coated tablets*

Ciproxin 50 mg/mL, oral suspension*

Ciproxin 100 mg/mL, oral suspension**

Ciproxin 2 mg/mL, solution for infusion*

*currently unavailable

** currently available

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 Film-coated tablets

Ciproxin 250 mg:

1 tablet contains 291 mg ciprofloxacin hydrochloride, corresp. to 250 mg ciprofloxacin as monohydrate

Ciproxin 500 mg:

1 tablet contains 582 mg ciprofloxacin hydrochloride, corresp. to 500 mg ciprofloxacin as monohydrate

Ciproxin 750 mg:

1 tablet contains 873 mg ciprofloxacin hydrochloride, corresp. to 750 mg ciprofloxacin as monohydrate

2.2 Oral suspension

Ciproxin 50 mg/mL:

1 bottle consists of 7.95 g of microcapsules which contain 5.0 g ciprofloxacin

1 bottle with 99.2 g suspension diluent to prepare 100 mL of Ciproxin Suspension 5 %

1 measuring spoonful (approx. 5.0 mL) contains approx. 250 mg ciprofloxacin

One measuring spoon (5.0 mL suspension) contains approx. 1.4 g of sucrose

Ciproxin 100 mg/mL:

1 bottle consists of 15.9 g of microcapsules which contain 10.0 g ciprofloxacin

1 bottle with 91.7 g suspension diluent to prepare 100 mL of Ciproxin Suspension 10 %

1 measuring spoonful (approx. 5.0 mL) contains approx. 500mg ciprofloxacin

One measuring spoon (5.0 mL suspension) contains approx. 1.3 g of sucrose

2.3 Solution for infusion

Ciproxin 2 mg/mL:

1 glass bottle of 100 mL infusion solution contains 254.4 mg ciprofloxacin lactate, corresp. to 200 mg ciprofloxacin. Sodium chloride content is 900 mg .

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

3. PHARMACEUTICAL FORM

3.1 Film-coated tablet

Ciproxin 250 mg:

Round, nearly white to slightly yellowish film-coated scored tablets marked with “CIP 250” on one side and a “Bayer cross” on the reverse side. The tablet can be divided into equal halves.

Ciproxin 500 mg:

Oblong, nearly white to slightly yellowish film-coated scored tablets marked with “CIP 500” on one side and a “Bayer” on the reverse side. The tablet can be divided into equal halves.

Ciproxin 750 mg:

Oblong, nearly white to slightly yellowish film-coated tablets marked with “CIP 750” on one side and a “Bayer” on the reverse side.

3.2 Oral suspension

Ciproxin 50 mg/mL:

Granules: white to slightly yellowish granules

Solvent: white to slightly yellowish suspension (with strawberry odour)

Ciproxin 100 mg/mL:

Granules: white to slightly yellowish granules

Solvent: white to slightly yellowish suspension (with strawberry odour)

Appearance before reconstitution: For the appearance of the reconstituted oral suspension, see *section 4.2.2 Method of administration*.

3.3 Solution for infusion

Ciproxin 2 mg/mL (with 0.9% NaCl)

Clear, nearly colourless to slightly yellowish solution.

The pH-value of the solution for infusion ranges from 3.9 to 4.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

4.1.1 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.

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.

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

4.1.2 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.

4.2.1 Dose

4.2.1.1 Adults

Unless otherwise prescribed, the following guideline doses are recommended:

	Tablets	**Suspension 5%**	**Suspension 10%**	**Intravenous**
Respiratory tract infection (according to severity and organism)	2 x 250-500mg	2 x 1-2*	2 x ½ -1*	2 x 200-400mg
Urinary tract infections: - acute, uncomplicated	1-2 x 250mg	2 x ½* to 1-2 x 1*	-	2 x 100mg
- cystitis in women (before menopause)	single dose 250mg	1 x 1*	1 x ½*	single dose 100mg
- complicated	2 x 250-500mg	2 x 1-2*	2 x ½ - 1*	2 x 200mg
Gonorrhoea - extragenital	1 x 250mg	-	-	2 x 100mg
- acute, uncomplicated	single dose 250mg	1 x 1*	1 x ½*	single dose 100mg
Diarrhoea	1-2 x 500mg	1-2 x 2*	1-2 x 1*	2 x 200mg
Other infections (see *section 4.1 Therapeutic*	2 x 500mg	2 x 2*	2 x 1*	2 x 200-400mg
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 750mg	2 x 3*	2 x 1 ½*	3 x 400mg
Inhalational anthrax (post- exposure) Drug administration should begin as soon as possible after suspected or confirmed exposure	2 x 500mg	2 x 2*	2 x 1*	2 x 400mg

* Number of measuring spoonful

4.2.1.2 Paediatric population

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) or 10 mg/kg iv three times daily (maximum daily dose 1200mg).

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). For intravenous infusion, the recommended dose is 10 mg/kg twice daily (not to exceed a maximum dose of 400 mg per dose, 800 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 6 to 10 mg/kg i.v. every 8 hours with a maximum of 400 mg per dose or 10 to 20 mg/kg orally every 12 hours with a maximum of 750 mg per dose.

4.2.2 Method of administration

4.2.2.1 Film-coated tablets

The tablets are swallowed whole with a small amount of fluid.

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, and 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.

4.2.2.2 Suspension

Oral suspension can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly. In this case, the suspension should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt, and 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 suspension, 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.

The reconstituted product is a white to slightly yellowish suspension with strawberry odour. Occasionally the suspension may contain yellow-orange droplets and globular particles. This has no influence on the pharmaceutical quality of the product.

Always use the graduated measuring spoon to obtain the exact dose for administering the suspension.

No additions should be made to the mixed final ciprofloxacin suspension.

4.2.2.3 Intravenous

Ciprofloxacin should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9 - 4.5). Only clear solutions are to be used.

For instructions on use of the medicine before administration, see *section 6.6 Special precautions for disposal*.

4.2.2.4 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:

Adults

- 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)
- 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.

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.

4.2.2.5 Missed dose

If a dose is missed, it should be taken as soon as the patient remembers and then treatment should be continued as prescribed. Double doses should not be taken to compensate for a missed dose.

4.2.3 Additional information on special populations

4.2.3.1 Elderly

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

4.2.3.2 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 for oral administration or 800 mg per day for an intravenous regimen.

1.2 Where creatinine clearance 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 for oral administration or 400 mg per day for an intravenous regimen.

2. Impaired renal function + haemodialysis
   Dose as in 1.2; on dialysis days after dialysis.
3. Impaired renal function + continuous ambulatory peritoneal dialysis (CAPD)
   a. Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin / litre dialysate administered 4 times a day every 6 hours
   b. 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 1.1 and 1.2

Children

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

4.3 Contraindications

Hypersensitivity to ciprofloxacin or other quinolone or any of the excipients (see *section 6.1 List of excipients*)

Concurrent administration of Ciproxin and tizanidine (see section 4.5 Interaction with other medicinal products and other forms of interaction)

4.4 Special warnings and precautions for use

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially persistent adverse reactions involving different body systems that have occurred together in the same patient. These include, but are not limited to, serious adverse reactions involving the nervous system (*see precautions regarding Seizures, Psychiatric reactions and*

Peripheral neuropathy in section 4.4 Special warnings and precautions for use) and musculoskeletal system (see *precautions regarding Myasthenia gravis and Tendinitis and tendon rupture in 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, Ciproxin should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections

Ciproxin is not recommended for treatment of pneumococcal infections due to limited efficacy against Streptococcus pneumoniae.

Genital tract infections

Genital tract infections may be caused by fluoroquinolone-resistant Neisseria gonorrhoea isolates. In genital tract infections thought or known to be due to N. gonorrhoea, 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

Ciproxin is associated with cases of QT prolongation (see *section 4.8 Undesirable effects*). As women tend to have a longer baseline QTc interval compared with men, they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using Ciproxin 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 Interaction with other medicinal products and other forms of interaction*') or in patients with risk factors for QT prolongation or torsade de pointes (e.g. congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalemia or hypomagnesemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Children and adolescents

As with medicinal products in its class, Ciproxin has been shown to cause arthropathy in weight-bearing joints of immature animals (see *section 4.8 Undesirable effects*). 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 drug related cartilage or articular damage. The use of Ciproxin 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 Ciproxin 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 (see *section 4.8 Undesirable effects*). 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 (see *section 4.8 Undesirable effects*). In these cases Ciproxin has to be discontinued, and 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 (see *section 4.8 Undesirable effects*). In such cases Ciprofloxacin must be discontinued and appropriate therapy initiated (e. g. vancomycin, orally, 4 x 250 mg/day). Drugs that inhibit peristalsis are contraindicated in this situation.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see *section 4.8 Undesirable effects*). There can be temporary increase in transaminases alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with Ciproxin (see *section 4.8 Undesirable effects*).

Myasthenia gravis

Ciproxin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (predominantly Achilles tendon) sometimes bilateral, may occur with Ciproxin, even within the first 48 hours of treatment. Cases occurring up to several months after completion of therapy have been reported. The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and in patients with solid organ transplants.

At any sign of tendinitis (e.g. painful swelling, inflammation), the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued. Ciproxin should be used with caution in patients with a history of tendon disorders related to fluoroquinolone treatment.

Seizures

Ciproxin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. 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), Ciproxin should only be used where the benefits of treatment exceed the risks, since these patients are at risk because of possible undesirable

CNS effects. Cases of status epilepticus have been reported (see *section 4.8 Undesirable effects*). If seizures occur, Ciproxin should be discontinued.

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including Ciproxin. In rare cases depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behaviour, such as attempted or completed suicide (see *section 4.8 Undesirable effects*). In the event that the patient develops these reactions, Ciproxin should be discontinued and the appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in parasthesias, hypoesthesias, dysethesias, or weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Patients under treatment with Ciproxin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness or weakness develop (see *section 4.8 Undesirable effects*).

Skin and appendages

Ciproxin has been shown to produce photosensitivity reactions. Patients taking Ciproxin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e. sunburn-like skin reactions) occurs (see *section 4.8 Undesirable effects*).

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, ropinirole, clozapine, olanzapine, agomelatine). Increased plasma concentrations associated with drug specific undesirable effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see *section 4.5 Interaction with other medicinal products and other forms of interaction).*

Dysglycaemia

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

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or

dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (eg 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.

Injection site reaction

Local i.v. site reactions have been reported with the intravenous administration of Ciprofloxacin (see *section 4.8 Undesirable effects*). These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Interaction with tests

Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium* tuberculosis culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Ciproxin.

Sucrose load for suspension formulation

As the oral suspension contains sucrose, it is unsuitable for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency (see *section 2 Qualitative and Quantitative composition.)*

NaCl load for i.v. formulation (bottles)

The additional sodium load should be taken into account when using Ciproxin IV in patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) See *section 2 Qualitative and Quantitative composition* for sodium content.

4.5 Interaction with other medicines and other form of interaction

Drugs known to prolong QT interval

Ciproxin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see *section 4.4 Special warnings and precautions for use)*.

Chelation complex formation

The simultaneous administration of Ciproxin (oral) and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids and highly buffered drugs (e.g. didanosine tablets), containing magnesium, aluminium, or calcium reduce the absorption of ciprofloxacin. Consequently, Ciproxin 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 H_2 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 oral Ciproxin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

Probenecid

Probenecid interferes with renal secretion of Ciproxin. Co-administration of probenecid containing medicinal products and Ciproxin increases the ciprofloxacin serum concentrations.

Omeprazole

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

Theophylline

Concurrent administration of Ciproxin and theophylline containing medicinal products 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 (see *Cytochrome P450* section in *4.4 Special warnings and precautions for use*).

Other xanthine derivatives

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

Phenytoin

Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related adverse effects when Ciproxin 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 Ciproxin with phenytoin.

NSAID

Animal studies have shown that the combination of very high doses of fluoroquinolones (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 Ciproxin 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 Ciproxin 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 Ciproxin with a Vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciproxin 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 Ciproxin therapy is indicated.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) 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 Ciproxin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect (see *Cytochrome P450* section in *4.5 Special warnings and precautions for use*). Tizanidine must not be administered together with ciprofloxacin (see *section 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 (see *Cytochrome P450* section in *4.4 Special warnings and precautions for use).*

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 Ciproxin (see *Cytochrome P450* section in *4.4 Special warnings and precautions for use*).

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 administration of 250 mg Ciproxin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with Ciproxin are advised (see *Cytochrome P450* section in *4.4 Special warnings and precautions for use*).

Sildenafil

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

Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a large increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see *Cytochrome P450 section 4.4 Special warnings and precautions for use*).

Zolpidem

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

4.6 Fertility, pregnancy and lactation

4.6.1 Fertility

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.

4.6.2 Pregnancy

The data that are available from the use of Ciproxin in pregnant women, indicate neither malformative nor feto/neonatal toxicity. Animal studies do not indicate reproductive toxicity. Based on animal studies, it cannot be excluded that the drug could cause damage to articular cartilage in the immature foetal organism (see *section 5.3 Preclinical safety data*), therefore the use of Ciproxin is not recommended during pregnancy.

Animal studies have not shown any evidence of teratogenic effects (malformations) (see *section 5.3 Preclinical safety data*).

4.6.3 Breast-feeding

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, the use of Ciproxin is not recommended during breast-feeding (see *section 5.3 Preclinical safety data*).

4.7 Effects on ability to drive and use machines

Fluoroquinolones including Ciproxin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (see *section 4.8 Undesirable effects*). This applies particularly in combination with alcohol.

4.8 Undesirable effects

4.8.1 Summary of the safety profile

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

4.8.2 Tabulated list of adverse reactions

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

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”

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumour cerebri)	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			Dyspnoea (including asthmatic condition)		

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
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 Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions	Injection site reaction[#]	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase		International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see *section 4.4 Special warnings and precautions for use*').

[#] For Ciproxin Solution for Infusion only.

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

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

4.8.3 Additional information on special populations

4.8.3.1 Pediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see *section 4.4 Special warnings and precautions for use*).

4.8.4 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 to https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported in some cases.

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (< 10 %) is eliminated by 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 fluoroquinolone antibacterial agent (ATCCODE: J 01 MA 02).

5.1.1 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.

5.1.2 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 fluoroquinolone 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. 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 drugs 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 least 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.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi

Haemophilius influenzae
Legionella spp.
Moraxella catarrhalis
Neisseria meningitidis
Pasteurella spp.
Salmonella spp.
Shigella spp.
Vibrio 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, Enterobacter 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 and intravenous regimens (see *section 4.2 Dose 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 drug administration period.

5.2 Pharmacokinetic properties

5.2.1 Absorption

5.2.1.1 Film-coated tablets

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of Ciproxin 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)	250 mg	500 mg	750 mg
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.

5.2.1.2 Oral Suspension

The pharmacokinetics of Ciproxin oral suspension 5% and 10% are virtually identical to those of tablets.

5.2.1.3 Solution for Infusion

Following an intravenous infusion of Ciproxin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400mg administered intravenously.

	Mean Ciprofloxacin Serum Concentrations (mg/l) after Intravenous Administration [Time from start of infusion (in hours)]
Time (h)	200mg i.v. (30 min inf.)
0.50	3.4
0.75	1.40
1.00	1.00
1.50	0.70
2.50	0.50
4.50	0.30
8.50	0.10
12.50	0.10

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin both given every 12 hours produced an equivalent area under the serum concentration time curve (AUC).

5.2.2 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.

5.2.3 Biotransformation

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.

5.2.4 Elimination

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
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

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. In 10 children with severe sepsis, less than 1 year of age C_{max} was 6.1 mg/L (range 4.6 – 8.3 mg/L) after a 1-hour intravenous infusion at a dose level of 10 mg/kg; and 7.2 mg/L (range 4.7 – 11.8 mg/L) for children between 1 and 5 years of age. The AUC-values were 17.4 mg*h/L (range 11.8 – 32.0 mg*h/L) and 16.5 mg*h/L (range 11.0 – 23.8 mg*h/L) in the respective

age groups. These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4 –5 hours and the bioavailability of the oral suspension approx. 60%.

5.3 Preclinical safety data

The **acute toxicity** of ciprofloxacin after oral administration can be classified as very low. Depending on the individual species, the LD_{50} after intravenous infusion is 125-290 mg/kg.

Species	**Mode of administration**	**LD_{50} (mg/kg)**
Mouse	p.o.	Approx. 5000
Rat	p.o.	Approx. 5000
Rabbit	p.o.	Approx. 2500
Mouse	i.v.	Approx. 290
Rat	i.v.	Approx. 145
Rabbit	i.v.	Approx. 125
Dog	i.v.	Approx. 250

5.3.1 Chronic Toxicity

5.3.1.1 Subacute tolerability studies over 4 weeks

Oral administration

Doses up to and including 100 mg/kg were tolerated without damage by rats. Pseudoallergic reactions due to histamine release were observed in dogs.

Parental administration

In the highest-dose group in each case (rats 80 mg/kg and monkeys 30 mg/kg), crystals containing ciprofloxacin were found in the urine sediment. There were also changes in individual renal tubules, with typical foreign-body reactions due to crystal-like precipitates.

The tubular changes observed should not (as e.g. in the case of aminoglycosides) be interpreted as a primary toxic effect of ciprofloxacin, but as secondary inflammatory foreign-body reactions due to the precipitation of a crystalline complex in the distal renal tubule system (cf. also the subchronic and chronic tolerability studies).

5.3.1.2 Subchronic Toxicity Studies over 3 months

Oral administration

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).

Parental administration

Although the changes in the renal tubules observed in rats were in some cases very slight, they were present in every dose group. In monkeys they were found only in the highest-dose group (18 mg/kg) and were associated with slightly reduced erythrocyte counts and haemoglobin values.

5.3.1.3 Chronic tolerability studies over 6 months

Oral administration

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).

Parental administration

In monkeys slightly elevated urea and creatinine concentrations and changes in the distal renal tubules were recorded in the highest-dose group (20 mg/kg).

5.3.2 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.

5.3.3 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.

5.3.4 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.

5.3.5 Renal tolerability

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

Compared to rapid infusion, a slow infusion of ciprofloxacin reduces the danger of crystal precipitation.

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.

5.3.6 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.

5.3.7 Studies aimed at excluding cataractogenic effects

On the basis of the investigations it may be stated from a toxicological point of view that Ciproxin 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.

5.3.8 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.1.1 Film-coated tablets

Microcrystalline cellulose

Maize starch

Poly (1-vinyl-2-pyrrolidone) crosslinked

Highly dispersed silicon dioxide

Magnesium stearate

Methylhydroxypropylcellulose

Macrogol 4000

Titanium dioxide (E171)

6.1.2 Suspension

Copolymer of ethyl acrylate

Methyl methacrylate

Magnesium stearate

Methylhydroxypropylcellulose

Polysorbate

Polyvidone

Lecithin

Sucrose

Strawberry flavour

Medium chain triglycerides

Water

6.1.3 Infusion solution

Lactic acid

Sodium chloride

Hydrochloric acid

Water for injection

6.2 Incompatibilities

Ciproxin IV solution

The Ciproxin infusion solution is compatible with physiological saline, Ringer solution and Ringer lactate solution, 5% and 10% glucose solutions, 10% fructose solution, and 5% glucose solution with 0.225% NaCl or 0.45% NaCl. When Ciproxin infusion solutions are mixed with compatible infusion solutions, they should be administered shortly after admixture for microbiological and light sensitivity reasons.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration. Only clear solutions are to be used

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillin's, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.9-4.5).

Oral suspension

No additions should be made to the mixed final ciprofloxacin suspension.

6.3 Shelf life

Ciproxin 250, 500, 700 film-coated tablets: 60 months

Ciproxin 50 mg/mL, 100 mg/mL oral suspension:

- Microcapsule: 36 months
- suspension diluent: 24 months

Shelf life of the reconstituted oral suspension: 14 days

The ready-to-use oral suspension utilizing these individual components is stable only for 14 days when stored either at ambient temperatures up to 30 °C, or in a refrigerator. After this time, the reconstituted oral suspension should not be taken. Protect the reconstituted oral suspension from freezing.

Ciproxin 2 mg/mL (with 0.9% NaCl) Infusion solution: 48 months

6.4 Special precautions for storage

Ciproxin Suspension

Microcapsule: Stored below 25 °C.

Suspension diluent: Stored below 25 °C. Protect from freezing. Avoid inverted storage.

For storage conditions after reconstitution of the medicine, see section *6.3 Shelf life*.

Ciproxin IV solution

Protect from light. Do not refrigerate or freeze.

At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion solution in a refrigerator.

Since the infusion solution is photosensitive, the infusion bottles should be removed from the box only immediately before use. In daylight conditions complete efficacy is guaranteed for a period of 3 days.

6.5 Nature and contents of container

Ciproxin 250, 500, 700 film-coated tablets: Foil, Strips of 14

Ciproxin 50 mg/mL, 100 mg/mL oral suspension: bottle, PET

Ciproxin 2 mg/mL (with 0.9% NaCl) Infusion solution: glass bottle

6.6 Special precautions for disposal and other handling

6.6.1 Instructions for use / handling

Ciproxin Suspension

The small bottle contains the active substance, the large bottle contains the suspension fluid. Open both bottles.

Reconstitution:

- Childproof cap: Press down according to instructions on the cap while turning to the left.
- Pour the microcapsules completely into the large bottle with the suspension fluid. Do not pour water into the suspension!
- Reclose the large bottle properly according to the instructions on the cap and shake vigorously for about 15 seconds. The suspension is now ready to use.

Taking the ready-to-use suspension.

Take the prescribed amount of suspension by using the measuring spoon. Do not chew the microcapsules present in the suspension, simply swallow them. A drink of water may be taken afterwards. Reseal the bottle properly after use according to the instructions on the cap. The ready- to-use suspension is stable for 14 days when stored in a refrigerator or at ambient temperatures below 30°C. After treatment has been completed, discard any surplus suspension. **Shake vigorously each time before use for approx. 15 seconds**

The graduated measuring spoon with the markings 1/2 is equivalent to 2.6 mL contains 2.5 mL of final suspension and 1/1 is equivalent to 5.2 mL contains 5.0 mL of final suspension. The graduated measuring spoon must be used for measuring the required prescribed amount of Ciproxin Suspension 5 % or 10%.

After use the graduated measuring spoon should be cleaned under running water with detergent rinsed with water and dried thoroughly afterwards.

Ciproxin IV solution

For glass bottles: For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

6.6.2 Special precautions for use

Ciproxin Suspension

Each consists of two individual components, Microcapsules and Suspension diluent. These should not be used after the expiration date has been reached.

Occasionally a slight yellow layer is observed on the surface of the sugar in the suspension. This has no influence on the pharmaceutical quality of the product.

The ready-to-use oral suspension utilizing these individual components is stable only for 14 days when stored either at ambient temperatures up to 30 °C, or in a refrigerator. After this time, the reconstituted oral suspension should not be taken. Protect the reconstituted oral suspension from freezing.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Bayer New Zealand Limited
3 Argus Place
Hillcrest
North Shore
Auckland 0627

Free Phone 0800 229 376

9. DATE OF FIRST APPROVAL

4 February 1988

10. DATE OF REVISION OF THE TEXT

1 October 2019

Summary table of changes

Section changed	Summary of new information
All	Update to the new Data Sheet format
4.1	Addition of statement: 'Consideration should be given to available official guidance on the appropriate use of antibacterial agents'
4.4	Additional safety warnings fluoroquinolones associated with disabling and potentially persistent adverse reactions involving different body systems Rephrasing of a statement related to psychiatric reactions and cardiac disorders Addition of "Agomelatine" to paragraph 'Cytochrome P450'
4.5	Addition of interaction with "Zolpidem" and "Agomelatine"
4.8	Referencing of specific terms 'arthralgia, arthritis' from the ADR table in section
6.6	Addition of cleaning advice for the spoon used for ciprofloxacin oral suspension
2.1, 2.2, 2.3	Information updated to correspond with product labels and Medsafe product details
4.2	Addition of information regarding missed doses
4.4	New headings for precautions relating to 'Myasthenia gravis', 'Tendinitis and tendon rupture', 'Seizures', 'Psychiatric reactions' and 'Peripheral neuropathy'
	Addition of risk factors for tendon disorders
	Addition of precaution regarding 'Dysglycaemia' and 'Aortic aneurysm and dissection'

	Reference to Tizanidine removed from sentence regarding Cytochrome P450 and concurrent medications because concurrent use is contraindicated
4.5	Conversion of information on concomitant use with Oral antidiabetic agents from an 'interaction' into a 'precaution' in Section 4.4
4.8	Addition of statement regarding potential for long-lasting adverse effects
6.6	Update cleaning advice for measuring spoon
1.0, 4.2, 4.4, 4.5, 4.8, 5.1, 6.6, 8.0	Multiple editorial changes