NEW ZEALAND DATA SHEET

CIPFLOX

1. Product Name

CIPFLOX 250 mg, 500 mg and 750 mg, film-coated tablets.

CIPFLOX INFUSION, 2 mg/mL, solution for infusion.

2. Qualitative and Quantitative Composition

Each film-coated tablet contains 250 mg, 500 mg or 750 mg of ciprofloxacin.

Each 100 mL bag of infusion contains 200 mg of ciprofloxacin and each 200 mL bag of infusion contains 400 mg of ciprofloxacin.

For the full list of excipients, see section 6.1.

This product is not able to deliver all approved dose regimens.

3. Pharmaceutical Form

CIPFLOX 250 mg tablets: White bi-convex round, film-coated tablets marked “CF”, “250” on either side of a score line on one side and “G” on the other side. The score line is not intended for breaking the tablet.

CIPFLOX 500 mg tablets in blisters: White bi-convex capsule shaped, film-coated tablets marked “CF”, “500” on either side of a score line on one side and “G” on the other side. Scored CIPFLOX 500 mg tablets can be divided into equal doses.

CIPFLOX 500 mg tablets in bottles: White bi-convex capsule shaped, film-coated tablets debossed with “G” on one side of the tablet and “CF 500” on the other side. Unscored CIPFLOX 500 mg tablets must not be halved.

CIPFLOX 750 mg tablets: White bi-convex capsule shaped, film-coated tablets marked “CF”, “750” on either side of a score line on one side and “G” on the other side. The score line is not intended for breaking the tablet.

CIPFLOX INFUSION, 2 mg/mL infusion: Clear, odourless, sterile solution in a plastic bag. The pH-value of the solution for infusion ranges from 3.5 to 4.6.

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.

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.

Children

Cystic fibrosis

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

Dose

Adults

Unless otherwise prescribed, the following guideline doses are recommended:

	Tablets	**Intravenous**
Respiratory tract infection (according to severity and organism)	2 x 250 - 500 mg	2 x 200 - 400 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 mg	 2 x 100mg single dose 100 mg 2 x 200 mg
Gonorrhoea - extragenital - acute, uncomplicated	 1 x 250 mg single dose 250 mg	 2 x 100 mg single dose 100 mg
Diarrhoea	1 - 2 x 500 mg	2 x 200 mg
Other infections (see section 4.1)	2 x 500 mg	2 x 200 - 400 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	3 x 400 mg
Inhalational anthrax (post-exposure) Drug administration should begin as soon as possible after suspected or confirmed exposure	2 x 500 mg	2 x 400 mg

Special populations

Paediatric

Cystic Fibrosis

Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (aged 5 to 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 i.v. three times daily (maximum daily dose 1200 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). 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.

Elderly

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

Renal and Hepatic impairment

Adults

1. Impaired renal function

    1.1. Where estimated glomerular filtration rate (eGFR) is between 30 and 60 mL/min/1.73 m^2 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 eGFR is equal or is less than 30 mL/min/1.73 m^2 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)

    3.1. Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin / litre dialysate administered 4 times a day every 6 hours.

    3.2. 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.

Method of administration

Oral

CIPFLOX 250 mg and 750 mg tablets should be swallowed whole with a small amount of fluid. Unscored CIPFLOX 500 mg tablets must also be swallowed whole with a small amount of liquid. Scored CIPFLOX 500 mg tablets may be halved and swallowed with a small amount of liquid.

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 the 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.

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: 3.5 - 4.6). Only clear solutions are to be used.

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)
- and 7 to 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

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.

Children

Cystic fibrosis

For acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients (aged 5 to 17 years), the duration of treatment is 10 to 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 to 21 days.

4.3 Contraindications

Hypersensitivity to ciprofloxacin or other quinolone or to any of the excipients listed in section 6.1.

Concurrent administration of ciprofloxacin and tizanidine (see section 4.5).

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) and musculoskeletal system (see precautions regarding Myasthenia gravis and Tendinitis and tendon rupture in section 4.4).

May cause tendonitis, hypoglycaemia.

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcus infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoea* isolates.

Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is

all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections

There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea

The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints

Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax

Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Paediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

Ciprofloxacin has been shown to cause arthropathy in weight- bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue (see section 4.8).

Broncho-pulmonary infections in cystic fibrosis

Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatment cannot be used, and should be based on the results of the microbiological documentation. Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatment cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.

The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience if limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

Prolonged, disabling and potentially irreversible serious adverse drug reaction

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluroquinolones and have been reported to occur even. up to several months after discontinuation of treatment (see section 4.8). The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation), the treatment with ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with myasthenia gravis

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

Aortic aneurysm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in the elderly population, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8)

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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:
- for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally
- for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- for heart valve regurgitation/incompetence (e.g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Vision disorder

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Photosensitivity

Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Seizures

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur, ciprofloxacin should be discontinued (see section 4.8).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Psychiatric reactions

Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts culminating in attempted or completed suicide. If depression, psychotic reactions, suicide-related thoughts or behaviour occur, ciprofloxacin should be discontinued.

Cardiac disorders

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction or bradycardia).

Elderly patients and woman may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations. (See section 4.2, 4.5, 4.8 and 4.9)

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in elderly diabetic patients, receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Gastrointestinal system

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system

Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

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). There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage, who are treated with ciprofloxacin (see section 4.8).

Glucose-6-phosphate dehydrogenase deficiency

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

Resistance

During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5). Co-administration of ciprofloxacin and tizanidine is contra-indicated.

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

Injection site reaction

Local i.v. site reactions have been reported with the intravenous administration of ciprofloxacin (see section 4.8). 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.

Interference with laboratory tests

The *in vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

4.5 Interaction with other medicines and other forms of interaction

Effects of other products on ciprofloxacin

Drugs known to prolong QT interval

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

Chelation complex formulation

The simultaneous administration of ciprofloxacin (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, ciprofloxacin should be administered either 1 to 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 ciprofloxacin 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 ciprofloxacin. Co-administration of probenecid containing medicinal products and ciprofloxacin increases ciprofloxacin serum concentrations.

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.

Omeprazole

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

Effects of ciprofloxacin on other medicinal products

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 section 4.3).

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline containing medicinal products can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline-induced side effects that may be life threatening or fatal. During the combination, serum theophylline concentration should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

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

Phenytoin

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

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.

Ciclosporin

A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin 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).

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 section 4.4).

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 an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products 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 ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

Sildenafil

C_{max} and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and 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 60-fold 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 in section 4.4).

Zolpidem

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

Levothyroxine

There are limited case reports that oral ciprofloxacin may decrease the absorption of levothyroxine. An interval of six hours between the administration of the two medications is recommended and monitoring to changes in thyroid function should be carried out.

4.6 Fertility, pregnancy and lactation

Pregnancy

The data that are available from the use of ciprofloxacin in pregnant women, indicate neither malformative nor feto/neonatal toxicity. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism/foetus (see section 5.3). As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Breast-feeding

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, the use of ciprofloxacin is not recommended during breast-feeding.

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.

4.7 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 (see section 4.8). This applies particularly in combination with alcohol.

4.8 Undesirable effects

Adverse effects with ciprofloxacin (oral and parenteral) sorted by CIOMS III categories of frequency are listed below.

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. 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)	
Immune system disorders			Allergic reaction, Allergic oedema / angiooedema	Anaphylactic reaction, Anaphylactic shock (life-threatening), Serum sickness-like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders		Decreased appetite and food intake	Hyperglycaemia, Hypoglycaemia		Hypoglycaemic coma

System organ class	Common	Uncommon	Rare	Very Rare	Not Known
Psychiatric disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation, Anxiety reaction, Abnormal dreams, Depression (potentially culminating in suicidal ideations / thoughts or suicide attempts and completed suicide), Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations / thoughts or suicide attempts and completed suicide)	Mania, including hypomania
Nervous system disorders		Headache, Dizziness, Sleep disorders, Taste disorders	Par- and Dysaesthesia, Hypoaesthesia, Tremor, Seizures (including status epilepticus), Vertigo	Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorders, Hyperesthesia, Intracranial hypertension (pseudotumour cerebri)	Peripheral neuropathy and polyneuropathy
Eye disorders			Visual disturbances (e.g. diplopia)	Visual colour distortions	
Ear and labyrinth disorders			Tinnitus, Hearing loss / Hearing impaired		
Cardiac disorders			Tachycardia		ECG QT prolonged, Ventricular arrhythmia, Torsades de pointes[1]
Vascular disorders			Vasodilatation, Hypotension, Syncope	Vasculitis	
Respiratory, thoracic and mediastinal disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal disorders	Nausea, Diarrhoea	Vomiting, Gastrointestinal and abdominal pains, Dyspepsia, Flatulence	Antibiotic associated colitis (very rarely with possible fatal outcome)	Pancreatitis	
Hepatobiliary disorders		Increase in transaminase, Increased bilirubin	Hepatic impairment, Cholestatic jaundice, Hepatitis (non-infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	

System organ class	Common	Uncommon	Rare	Very Rare	Not Known
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), Drug reaction with eosinophilia and systemic symptoms (DRESS)
Musculoskeletal, connective tissue and bone disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), Arthralgia	Myalgia, Arthritis, Increased muscle tone and cramping	Muscular weakness, Tendonitis, Tendon rupture (predominantly Achilles tendon), Exacerbation of symptoms of myasthenia gravis	
Renal system disorders		Renal impairment	Renal failure, Haematuria, Crystalluria, Tubulointerstitial nephritis		
General disorders and administration site conditions	Injection site reaction[2]	Unspecific pain, Feeling unwell, Asthenia, Fever	Oedema, Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphate	Abnormal prothrombin level, Increased amylase		International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)

[1] These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

[2] For ciprofloxacin solution for infusion only.

Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

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

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Additional information on special populations

Paediatric 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).

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

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, 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.

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

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials,

ATC code: J01MA02

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibacterial agent.

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 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 inactivate 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	*Haemophilus 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, Enterococcus faecium, Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealyticum, Anaerobic microorganisms (except Mobiluncus, Peptostreptococcus, 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).

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~ 5.5 x 10^5) spores (range 5 to 30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 microgram/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 microgramg/mL. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 microgram/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

Absorption

Film-coated tablets

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 to 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 to 80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

Solution for infusion

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

	Mean ciprofloxacin serum concentrations (mg/l) after intravenous administration **[Time from start of infusion (in hours)]**
Time (h)	**200 mg 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).

Distribution

The protein binding of ciprofloxacin is low (20 to 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 to 3 L/kg body weight shows that ciprofloxacin penetrates into tissues resulting in concentrations which clearly exceed the corresponding serum levels.

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.

Elimination

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

Excretion of ciprofloxacin (% of dose)		
	Urine	**Faeces**
Oral administration		
Ciprofloxacin	44.7	25.0
Metabolites (M_1 – M_4)	11.3	7.5
Intravenous administration		
Ciprofloxacin	61.5	15.2
Metabolites (M_1 – M_4)	9.5	2.6

Renal clearance is between 0.18 to 0.3 L/h/kg and the total body clearance between 0.48 to 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 to 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 to 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 to 32.0 mg*h/L) and 16.5 mg*h/L (range 11.0 to 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 approximately 4 to 5 hours and the bioavailability of the oral suspension approximately 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 to 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

Chronic Toxicity

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.

Parenteral 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).

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).

Parenteral 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.

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).

Parenteral 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).

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.

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.

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.

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.

6. Pharmaceutical Particulars

6.1 List of excipients

CIPFLOX tablets

CIPFLOX 250 mg, 500 mg and 750 mg tablets also contain

- microcrystalline cellulose,
- maize starch,
- pregelatinised maize starch,
- crospovidone,

- colloidal anhydrous silica,
- magnesium stearate,titanium dioxide,
- polydextrose,
- hypromellose,
- glycerol triacetate,
- macrogol.

CIPFLOX infusion

CIPFLOX INFUSION, 2 mg/mL solution for infusion also contains

- lactic acid,
- glucose monohydrate,
- hydrochloric acid,
- water for injection.

6.2 Incompatibilities

The ciprofloxacin 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 ciprofloxacin 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. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.5 to 4.6).

6.3 Shelf life

CIPFLOX tablets

Blister pack: 3 years.

Bottle pack: 2 years.

CIPFLOX infusion

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

Since the infusion solution is photosensitive, the infusion bags should be removed from the overwrap only immediately before use.

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.

6.5 Nature and contents of container

CIPFLOX tablets

Blister pack, PVC/PVDC/Al foil. Pack sizes of 14 and 28 film-coated tablets.

White HDPE bottles with white screw caps. Pack size of 100 film-coated tablets.

Blue HDPE bottle with blue child resistant closure. Pack size of 100 film-coated tablets.

Not all pack types and sizes may be marketed.

CIPFLOX infusion

Polyolefin (non-PVC) bags with an opaque overwrap and packed in an outer carton in quantities of 10 x 100 mL and 10 x 200 mL.

Not all pack types and sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Viatris Ltd
PO Box 11-183
Ellerslie
AUCKLAND
www.viatris.co.nz
Telephone 0800 168 169

9. Date of First Approval

19 July 2001

10. Date of Revision of the Text

16 June 2022

Summary table of changes

Section	Summary of new information
4.2	Clarification for dose recommendations for patients with renal impairment