

NEW ZEALAND DATA SHEET

CIPFLOX

Ciprofloxacin, film coated tablets and infusion
100 mg, 250 mg, 500 mg, 750 mg and 2 mg/mL



Presentation

Cipflox 100mg tablets*: White bi-convex round, film-coated tablets marked “CF” on one side and “G” on the other side.

Cipflox 250mg 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.

Cipflox 500mg tablets: 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.

Cipflox 750mg 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.

Cipflox Infusion 2mg/mL*: 100mL bag of infusion solution contains 200mg ciprofloxacin and 200mL bag of infusion solution contains 400mg ciprofloxacin. The pH-value of the solution for infusion ranges from 3.5 to 4.6.

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

***Presentations currently not marketed in New Zealand**

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.

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.

Dosage and Administration

Recommended usual dose:

Adults

Unless otherwise prescribed, the following guideline doses are recommended:

	Tablets	Intravenous
Respiratory tract infection (according to severity and organism)	2 x 250-500mg	2 x 200-400mg
Urinary tract infections: - acute, uncomplicated - cystitis in women (before menopause) - complicated	1-2 x 250mg single dose 250mg 2 x 250-500mg	2 x 100mg single dose 100mg 2 x 200mg
Gonorrhoea - extragenital - acute, uncomplicated	1 x 250mg single dose 250mg	2 x 100mg single dose 100mg
Diarrhoea	1-2 x 500mg	2 x 200mg
Other infections (see Indications)	2 x 500mg	2 x 200-400mg
Particularly severe, life threatening infections, i.e. - <i>Streptococcal pneumonia</i> -Recurrent infections in cystic fibrosis -Bone and joint infections -Septicaemia -Peritonitis In particular when <i>Pseudomonas</i> , <i>Staphylococcus</i> or <i>Streptococcus</i> is present	2 x 750mg	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 400mg

Elderly

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

Children

Cystic Fibrosis

Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (aged 5 -17 years) with acute pulmonary exacerbation associated with *P. aeruginosa* infection, at a dose of 20 mg/kg orally twice daily (maximum daily dose 1500 mg) or 10 mg/kg iv three times daily (maximum 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.

Method of Administration

Oral

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, 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).

Duration of Treatment

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

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

In streptococcal infections the treatment must last at least 10 days because of the risk of late complications.

Infections caused by *Chlamydia* should also be treated for a minimum of 10 days.

Children

Cystic Fibrosis

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

Inhalation anthrax (post-exposure)

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

Complicated urinary tract infections and pyelonephritis

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

Renal & Hepatic impairment

Adults

1. Impaired renal function

- 1.1. Where creatinine clearance is between 30 and 60 mL/min/1.73m² or where the serum creatinine concentration is between 1.4 and 1.9 mg/100 mL the maximum daily dose should be 1000 mg per day for oral administration or 800 mg per day for an intravenous regimen.
- 1.2. Where creatinine clearance is equal or is less than 30 mL/min/1.73m² or where the serum creatinine concentration is equal or higher than 2.0 mg/100 mL the maximum daily dose should be 500 mg per day 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.

CONTRAINDICATIONS

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

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine-induced side effects (hypotension, somnolence, drowsiness) can occur.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Severe infections and/or infections due to Gram-positive or anaerobic bacteria

For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, ciprofloxacin should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections

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

Genital tract infections

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

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see **ADVERSE EFFECTS**). In general, elderly patients may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics) or in patients with risk factors for torsade de pointes (e.g., known QT prolongation, uncorrected hypokalemia).

Children and adolescents

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

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure)(see **PHARMACODYNAMIC PROPERTIES: INHALATIONAL ANTHRAX - ADDITIONAL INFORMATION**).

Hypersensitivity

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

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

Gastrointestinal System

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

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

Musculo-Skeletal System

Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment. Ciprofloxacin may cause tendonitis or tendon rupture. The risk of tendonitis or tendon rupture (predominantly Achilles tendon) is increased in patients over the age of 60 years; on concomitant systemic steroid therapy; who have received a kidney, heart or lung transplant. Ciprofloxacin should not be used in patients with a history of fluoroquinolone associated tendonopathy. Tendonitis and tendon rupture is present during use and for 6 months following use of ciprofloxacin.

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

Nervous System

In epileptics and in patients who have suffered from previous CNS-disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are at risk because of possible central-nervous side effects.

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

Skin and Appendages

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

Cytochrome P450

Ciprofloxacin is known to be a moderate inhibitor of the CYP450 1A2 enzymes. Care should be taken when other medicinal products are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. theophylline, methylxantines, caffeine, duloxetine, clozapine). Increased plasma concentrations associated with drug specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see **INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION**).

Injection Site Reaction

Local i.v. site reactions have been reported with the intravenous administration of ciprofloxacin. 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* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

Use in Pregnancy

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

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

Use in Lactation

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding (see **PRECLINICAL SAFETY DATA**).

Effects on Ability to Drive and Use Machines

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

ADVERSE 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.

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 postmarketing 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, Thrombocytæmia	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	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation, Anxiety reaction, Abnormal dreams, Depression, Hallucinations	Psychotic reactions	
Nervous System Disorders		Headache, Dizziness, Sleep disorders, Taste disorders	Par- and Dyaesthesia, Hypoaesthesia, Tremor, Seizures, Vertigo	Migraine, Disturbed coordination, Smell disorders, Hyperesthesia, Intracranial hypertension	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)		

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, Unspecific blistering	Petechiae, Erythema multiforme, Erythema nodosum, Stevens-Johnson syndrome (potentially life- threatening), Toxic epidermal necrolysis (potentially life- threatening)	
Musculoskeletal , Connective Tissue and Bone Disorders		Arthralgia	Myalgia, Arthritis, Increased muscle tone and cramping	Muscular weakness, Tendonitis, Tendon rupture (predominantly Achilles tendon), Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure, Haematuria, Crystalluria, Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Unspecific pain, Feeling unwell, Fever	Oedema, Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal, Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see **SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

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

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytæmia, 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

INTERACTIONS

Interaction with other medicinal products and other forms of interaction

Class IA or III antiarrhythmics

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

Chelation Complex 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 1-2 hours **before**, or at least 4 hours **after** these preparations.

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

Food and Dairy Products

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

Omeprazole

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

Theophylline

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

Other xanthine derivatives

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

NSAID

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

Cyclosporin

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

Vitamin K antagonists

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

Glibenclamide

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

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (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 ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (see **CONTRAINDICATIONS**).

Duloxetine

In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.

Ropinirole

In a clinical study it was shown that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.

Lidocaine

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

Clozapine

Following concomitant administration of 250 mg ciprofloxacin for 7 days, serum concentration of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

Sildenafil

C_{max} and AUC of sildenafil were increased approximately 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.

OVERDOSE

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

Therefore, apart from routine emergency measures, it is recommended to monitor renal function and to administer Mg- or Ca-containing antacids which reduce the absorption of ciprofloxacin.

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

FURTHER INFORMATION

Pharmacodynamic properties

Ciprofloxacin is a synthetic broad spectrum antibacterial agent (ATCCODE: J 01 MA 02).

Mechanism of Action

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

Mechanism of Resistance

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

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

<i>Aeromonas</i> spp.	<i>Moraxella catarrhalis</i>
<i>Brucella</i> spp.	<i>Neisseria meningitidis</i>
<i>Citrobacter koseri</i>	<i>Pasteurella</i> spp.
<i>Francisella tularensis</i>	<i>Salmonella</i> spp.
<i>Haemophilus ducreyi</i>	<i>Shigella</i> spp.
<i>Haemophilus influenzae</i>	<i>Vibrio</i> spp.
<i>Legionella</i> spp	<i>Yersinia pestis</i>

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 pediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**).

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD₅₀ (~5.5 x 10⁵) spores (range 5-30 LD₅₀) 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.

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 1-2 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.

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 400mg 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 (20-30%), and the substance is present in plasma largely in a non-ionised form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state volume of distribution of 2-3 L/kg body weight shows that ciprofloxacin penetrates into tissues resulting in concentrations which clearly exceed the corresponding serum levels.

Metabolism

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

Excretion

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

Excretion of Ciprofloxacin (% of dose)		
	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 0.18-0.3 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 metabolism. 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%.

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

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.

Reproduction toxicology

Fertility studies in rats

Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.

Embryotoxicity studies

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

Perinatal and postnatal development in rats

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

Mutagenicity

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin.

Test results are listed below:

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

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

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

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

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

Special tolerability studies

It is known from comparative studies in animals, both with the older gyrase inhibitors (e.g. nalidixic and piperidic 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.

PHARMACEUTICAL PRECAUTIONS

List of Excipients

Tablets: Cipflox 100 mg, 250 mg, 500 mg and 750 mg

Microcrystalline cellulose, pregelatinised maize starch, crospovidone, colloidal anhydrous silica, magnesium stearate, and Opadry White Y-22-7719

Infusion solution: Cipflox 2mg/mL

Lactic acid, glucose, hydrochloric acid, water for injection.

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.

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).

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

Special Precautions for Storage and Use

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.

PACKAGE QUANTITIES

Cipflox Tablets: Blister strip packs of 14 and 28 tablets

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 presentations and pack sizes may be marketed.

MEDICINE CLASSIFICATION

Prescription Medicine

SPONSOR DETAILS

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