New Zealand Datasheet

Name of Medicine

CIPROFLOXACIN

Ciprofloxacin hydrochloride tablets

Presentation

Ciprofloxacin tablets 250 mg: white, circular, biconvex, film-coated tablet, with a score and "CP 250" embossed on one side and plain on the other.

Ciprofloxacin tablets 500 mg: white, capsule shaped, film-coated tablet, with a score and "CPX 500" embossed on one side and "NEO embossed on the other.

Ciprofloxacin tablets 750 mg: white, capsule shaped, film-coated tablet, with "CPX 750" embossed on one side and "NEO embossed on the other.

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

Uses

Actions

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

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

In vitro Susceptibility to Ciprofloxacin

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

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

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

Aerobic Gram-Negative Microorganisms:
Aeromonas spp.
Moraxella catarrhalis
Brucella spp.
Neisseria meningitidis
Citrobacter koseri
Pasteurella spp.
Francisella tularensis
Salmonella spp.
Haemophilus ducreyi
Shigella spp.
Haemophilius influenzae
Vibrio spp.
Legionella spp.
Yersinia pestis

Anaerobic microorganisms
Mobiluncus

Other Microorganisms
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

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

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

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

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

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see Dosage and Administration).

A placebo-controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD_{50} (~5.5 x 10_5) spores (range 5-30 LD_{50}) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 µg/ml. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (1 hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 µg/ml. Mean steady-state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 µg/ml. Mortality due to anthrax for animals that received a 30-day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p = 0.001]. The one ciprofloxacin-treated animal that died of anthrax did so following the 30-day drug administration period.

Pharmacokinetics

Absorption:

Following oral administration of single doses of 250mg, 500mg, and 750mg 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 (Cmax) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose.

Distribution:

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

Metabolism:

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

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

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

Renal clearance is between 0.18-0.3 L/h/kg and the total body clearance between 0.48-0.60 L/h/kg. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Non-renal clearance of ciprofloxacin is mainly due to active transintestinal secretion as well as metabolisation. 1% of the dose is via the biliary excreted route. Ciprofloxacin is present in the bile in high concentrations.

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 drug 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, Neisseria, Moraxella, Acinetobacter, Brucella; Staphylococcus, Listeria, Corynebacterium, Chlamydia.*

The following show varying degrees of sensitivity:
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
For the treatment of acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients aged 5-17 years.

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

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

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

Children
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 20mg/kg orally twice daily (maximum daily dose 1500mg).

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

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

Method of Administration:
The tablets are swallowed whole with a small amount of fluid. Do not halve tablet. Dose equivalence when the tablet is divided has not been established.

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

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

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

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

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

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

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.

Inhalational 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 31 and 60 ml/min/1.73m² or where the se creatinine concentration is between 1.4 and 1.9 mg/100 ml the maximum daily dose shoul 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 se creatinine concentration is equal or higher than 2.0 mg/100 ml the maximum daily d should be 500 mg per day for oral administration or 400 mg per day for an intraven regimen.

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

Impaired renal function + CAPD
a) Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50

ciprofloxacin / litre dialysate administered 4 times a day every 6 ho
b) Administration of ciprofloxacin film coated tablets (oral) as 1 x 500 mg film coated tablet
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.

Concurrent administration of ciprofloxacin and tizanidine

Warnings and Precautions

May cause tendinitis, hypoglycaemia.

Severe infections and/or infections due to Gram-positive or anaerobic bacteria
For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, Ciprofloxacin tablets 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 and women may be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using Ciprofloxacin tablets with concomitant drugs that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics, see Interactions) or in patients with risk factors for QT prolongation or torsade de pointes (e.g., congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalemia or hypomagnesemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia.)

Children and adolescents
As with drugs 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 Uses – Actions: Inhalational Anthrax – Additional Information.

Cytochrome P450:
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other drugs are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. tizanidine, theophylline, methylxantines, caffeine, duloxetine, ropinirole, clozapine, olanzapine). Increased plasma concentrations associated with drug specific undesirable effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see Interactions).

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 in this situation.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see Adverse Effects). 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.

Nervous System:
Ciprofloxacin, like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. In epileptics and in patients who have suffered from previous CNS-disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke), ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are at risk because of possible undesirable central-nervous effects. Cases of status epilepticus have been reported. If seizures occur, ciprofloxacin should be discontinued.

Psychiatric reactions may occur after the first administration of fluoroquinolones, including Ciprofloxacin. In rare cases depression or psychotic reactions can progress to suicidal ideations/thoughts and self injurious behaviour such as attempted or completed suicide (see Adverse Effects. In these cases Ciprofloxacin should be discontinued and the appropriate measures instituted.

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

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.

Musculo-Skeletal System:
Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Tendinitis and tendon rupture (predominantly Achilles tendon) sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures or tendon may occur even up to several months after discontinuation of Ciproxin therapy. The risk of tendinopathy may be increase in elderly patients or in patients concomitantly treated with corticosteroids.

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

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

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) occur.

Use in Pregnancy
The data that are available from the use of ciprofloxacin in pregnant women, indicate neither malformative nor foeto/neonatal toxicity. Animal studies do not indicate reproductive toxicity. Based on animal studies, it cannot be excluded that the drug could cause damage to articular cartilage in the immature foetal organism (see Preclinical Safety Data), therefore the use of ciprofloxacin is not recommended during pregnancy. 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, the use of Ciprofloxacin tablets is not recommended during breast-feeding (see Preclinical Safety Data).

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

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

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

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

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		Eosinophilia	Leukopenia Anaemia Thrombocytaemia 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	
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic Reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial Hypertension (pseudotumour cerebri)	Peripheral neuropathy and polyneuropathy
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth			Tinnitus	Hearing impaired	

Disorders			Hearing loss		
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)	Acute generalised exanthematous pustulosis (AGEP
Musculoskeletal Connective Tissue and Bone Disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance	International Normalised Ratio (INR) increased (in patients treated with Vitamin K antagonists)
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase		

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see Warnings and Precautions).

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

Interactions

Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium*tubuerculosis. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking 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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Chelation Complex Formualtion
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 tabelts), containing magnesium, aluminium, or calcium reduce the absorption of ciprofloxacin. Consequently, Ciprofloxacin tablets 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.

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

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

Theophylline
Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline-induced

side effects; in very rare cases these side effects can be life threatening or fatal. If concurrent use of the two products is unavoidable, the serum theophylline concentration should therefore be checked and the theophylline dose appropriately reduced.

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

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

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 tablets 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 tablets with a Vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

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

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

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 tablets. 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 ropinirole-related side effects dose adjustment as appropriate is recommended during and shortly after co-administration with Ciprofloxacin tablets.

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

Clozapine
Following concomitant and administration or 250 mg Ciprofloxacin tablets 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 coadministration with Ciprofloxacin tablets 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 tablets. Therefore, caution should be used prescribing Ciprofloxacin tablets concomitantly with sildenafil taking into consideration the risks and the benefits.

Overdosage

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

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

Only a small quantity of ciprofloxacin (< 10 %) is eliminated by haemodialysis or peritoneal dialysis.

Pharmaceutical Precautions
Ciprofloxacin tablets should be stored in the original pack at less than 25°C.

Medicine Classification

Prescription Medicine.

Package Quantities

Ciprofloxacin tablets 250 mg: 30 tablets.
Ciprofloxacin tablets 500 mg: 30 tablets.
Ciprofloxacin tablets 750 mg: 30 tablets.

Further Information

Pre-clinical Safety Data

Acute toxicity:
The acute toxicity of ciprofloxacin after oral administration can be classified as very low. Depending on the individual species, the LD50 after intravenous infusion is 125-290 mg/kg.

Species	Mode of administration	LD50 (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 tolerability 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 b.w./day after 22 weeks), there was no evidence of a carcinogenic potential at any dose level.

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

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

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

Mutagenicity:
Eight in vitro mutagenicity tests have been conducted with ciprofloxacin.

Test results are listed below:

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

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

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

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

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

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

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

Excipients
Croscarmellose sodium, microcrystalline cellulose, povidone (K 30), magnesium stearate, colloidal silica, anhydrous, hypromellose, titanium dioxide, purified talc, propylene glycol, macrogol 6000

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