



APO-CIPROFLOXACIN

Ciprofloxacin 250mg, 500mg and 750mg tablets

Presentation

APO-CIPROFLOXACIN 250mg are white, round, biconvex film coated tablets, marked with “4” on one side and scored on the other side. Each tablet typically weighs 380mg with a diameter of 11.0mm.

APO-CIPROFLOXACIN 500mg are white, oblong film coated tablets marked “5” on one side and scored on the other side. Each tablet typically weighs 760mg and is 19.1mm long by 7.6mm wide.

APO-CIPROFLOXACIN 750mg are white, oblong film coated tablets marked “6” on one side. Each tablet typically weighs 1137mg and is 22.25mm long by 8.2mm wide.

Uses

Actions

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

Ciprofloxacin is effective in-vitro against virtually all gram-negative pathogens, including *Pseudomonas aeruginosa*. It is also effective against gram-positives such as staphylococci and streptococci. Anaerobes are generally less susceptible.

Ciprofloxacin has a rapid bactericidal action, not only in the proliferation phase but also in the resting phase.

During the proliferation phase of a bacterium a segmental twisting and untwisting of the chromosomes take place. An enzyme called DNA gyrase plays a decisive part in this process. Ciprofloxacin inhibits this DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.

Resistance to ciprofloxacin develops slowly and in stages (multiple-step type).

Plasmid-mediated resistance development of the kind that occurs with β -lactam antibiotics, aminoglycosides, and tetracyclines has not been observed with ciprofloxacin. It is of clinical interest that plasmid-carrying bacteria are also completely sensitive to ciprofloxacin.

On account of its different mode of action, parallel resistance to other important, chemically different, active substance groups, such as β -lactam antibiotics, aminoglycosides, tetracyclines, macrolide or peptide antibiotics, sulphonamides, trimethoprim or nitrofurans generally is not seen with Ciprofloxacin. In its indication area ciprofloxacin remains completely effective on pathogens resistant to the above-mentioned groups of antibiotics.

Parallel resistance is observed within the group of gyrase inhibitors. However, because of the high primary sensitivity to ciprofloxacin shown by most organisms parallel resistance is less pronounced with this drug. Ciprofloxacin is thus often still effective on pathogens that are already resistant to the less effective gyrase inhibitors.



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Because of its chemical structure ciprofloxacin is completely effective on β -lactamase-forming bacteria.

APO-CIPROFLOXACIN can be used in combination with another antibiotic. *In-vitro* studies with usually sensitive pathogens, carried out using ciprofloxacin in combination with β -lactam antibiotics and aminoglycosides, have shown primarily additive or indifferent effects; synergistic increases in efficacy were relatively rare and antagonistic effects very rare.

Possible combination drugs include:

for pseudomonas: azlocillin, ceftazidime

for streptococci: mezlocillin, azlocillin, other effective β -lactam antibiotics

for staphylococci: β -lactam antibiotics, particularly isoxazolympenicillins, vancomycin

for anaerobes: metronidazole, clindamycin

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.

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.

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

The oral administration of 250mg ciprofloxacin both given every 12 hours produced an equivalent area under the serum concentration time curve (AUC).

Results of pharmacokinetic studies in paediatric cystic fibrosis patients have shown dosages of 20mg/kg bd orally or 10mg/kg tid iv are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimens.

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.



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Bioavailability:

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



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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:

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

The following show varying degrees of sensitivity:

Alcaligenes	Mycobacterium fortuitum	Streptococcus agalactiae
Enterococcus faecalis	Mycobacterium tuberculosis	Streptococcus pneumoniae
Flavobacterium	Mycoplasma hominis	Streptococcus pyogenes
Gardnerella		Viridans group streptococci

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*.

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), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate.

The use of ciprofloxacin for indications other than those stated is not recommended in children.

Dosage and Administration

Recommended usual dose of APO-CIPROFLOXACIN tablets:



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Adults

Unless otherwise prescribed, the following guideline doses are recommended:

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

Elderly

Elderly patients should receive a dose as low as possible of APO-CIPROFLOXACIN 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.



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Method of Administration:

APO-CIPROFLOXACIN tablets should be 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.

Note: If a 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:

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. For inhalational anthrax (post-exposure), the duration of treatment is 60 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 serum creatinine concentration is between 1.4 and 1.9 mg/100 ml the maximum daily dose should be 1000mg per day for oral administration or 800mg 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 500mg per day for oral administration or 400mg per day for an intravenous regimen.
2. Impaired renal function + haemodialysis
Dose as in 1.2; on dialysis days after dialysis.



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- 3 Impaired renal function + CAPD
 - a) Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin / litre dialysate administered 4 times a day every 6 hours
 - b) Administration of ciprofloxacin film coated tablets (oral) as 1 x 500mg film coated tablet (or 2 x 250mg 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

APO-CIPROFLOXACIN must not be used in cases of hypersensitivity to ciprofloxacin or other quinolone chemotherapeutics.

APO-CIPROFLOXACIN must not be prescribed for pregnant women or nursing mothers as there is no experience regarding safety in these patient groups and since, on the basis of animal studies, it is possible that the drug could cause damage to articular cartilage in the foetus or infant.

Animal studies have not shown any evidence of teratogenic effects.

When considering treatment for inhalational anthrax (post-exposure), the risks and benefits of ciprofloxacin and alternative antibiotic therapies must be carefully considered, and explained to the patient.

Warnings and Precautions

APO-CIPROFLOXACIN may cause tendinitis, hypoglycaemia.

Paediatric Use:

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. 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 **Dosage and Administration**.



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The use of APO-CIPROFLOXACIN for indications other than the treatment of acute pulmonary exacerbation of cystic fibrosis caused by *P. aeruginosa* infection, and inhalational anthrax (post-exposure), is not recommended.

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 APO-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.

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), APO-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 APO-CIPROFLOXACIN. In rare cases depression or psychosis can progress to self endangering behaviour. In these cases APO-CIPROFLOXACIN has to be discontinued and the doctor should be informed immediately.

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 APO-CIPROFLOXACIN must be discontinued, medical treatment (e.g. treatment for shock) is required.

Musculo-Skeletal System:

At any sign of tendinitis (e. g. painful swelling) the administration of APO-CIPROFLOXACIN should be discontinued, physical exercise should be avoided, and a physician consulted.

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

Skin and Appendages:

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



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Hypoglycaemia:

Hypoglycaemia has been noted with enoxacin and lomefloxacin but it is not known whether it occurs with ciprofloxacin.

Use in Pregnancy and Lactation

Category B3

APO-CIPROFLOXACIN must not be prescribed for pregnant women, or nursing mothers, since there is no experience on the drug's safety in these patient groups and since, on the basis of animal studies, it is possible that the drug could cause damage to articular cartilage in the foetus or infant. Animal studies have not shown any evidence of teratogenic effects (malformations).

Affect on ability to drive and operate machinery

Even when APO-CIPROFLOXACIN is taken exactly as prescribed, it can affect the speed of reaction to such an extent that the ability to drive or to operate machinery is impaired. This applies particularly in combination with alcohol.

Adverse Effects

The most common Adverse Reactions based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency and COSTART (5th Edition, 1995) body system and terms (n = 41151 patients, status: 20.11.1997).

Body System

Incidence of frequency $\geq 1\%$ and $< 10\%$

Digestive system:

Skin and appendages:

Adverse Drug Reactions

nausea, diarrhoea

rash

Incidence of frequency $\geq 0.1\%$ and $< 1\%$

Body as a whole:

abdominal pain, moniliasis, asthenia (general feeling of weakness, tiredness)

Cardiovascular system:

(thrombo)-phlebitis

Digestive system:

SGOT increased, SGPT increased, vomiting, dyspepsia, abnormal liver function test, alkaline phosphatase increased, anorexia, flatulence, bilirubinemia

Haemic and lymphatic system:

eosinophilia, leucopenia

Injection site reaction:

injection site reaction

Metabolic and nutritional disorder:

creatinine increased, BUN (urea) increased



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Body System

Incidence of frequency $\geq 1\%$ and $< 10\%$

Musculo Skeletal system:

Nervous system:

Skin and appendages:

Special senses:

Adverse Drug Reactions

arthralgia (joint pain)

headache, dizziness, insomnia, agitation, confusion

pruritus, maculopapular rash, urticaria

taste perversion

Incidence of frequency $\geq 0.01\%$ and $< 0.1\%$

Body as a whole

Cardiovascular system:

Digestive system:

Haemic and lymphatic system:

Hypersensitivity:

Metabolic disorders:

Musculo-Skeletal system:

Nervous system:

Respiratory system:

Skin and appendages:

Special senses:

Urogenital system:

pain, pain in extremities, back pain, chest pain

tachycardia, migraine, syncope (fainting vasodilatation (hot flushes), hypotension

moniliasis (oral), jaundice, cholestatic jaundice, pseudomembranous colitis

anaemia, leucopenia (granulocytopenia), leucocytosis, altered prothrombin values, thrombocytopenia, thrombocytemia (thrombocytosis)

allergic reaction, drug fever, anaphylactoid (anaphylactic) reaction

edema (peripheral, vascular, face), hyperglycemia

myalgia (muscular pain), joint disorder (joint swelling)

hallucination, sweating, paresthesia (peripheral paralgesia), anxiety, abnormal dreams (nightmares), depression, tremor (trembling), convulsion, hypaesthesia

dyspnea, larynx edema

photosensitivity reaction

tinnitus, transitory deafness (especially at high frequencies), abnormal vision (visual disturbances), diplopia, chromatopsia, taste loss (impaired taste)

acute kidney failure, kidney function abnormal, vaginal moniliasis haematuria, crystalluria, nephritis interstitial

Incidence of frequency $< 0.01\%$

Cardiovascular system:

vasculitis (petechiae, haemorrhagic bullae, papules, crust formation)



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Body System

Incidence of frequency $\geq 1\%$ and $< 10\%$

Digestive system:

Haemic and lymphatic system:

Hypersensitivity:

Musculo-skeletal system:

Nervous system:

Skin and appendages:

Adverse Drug Reactions

moniliasis (gastrointestinal), hepatitis

haemolytic anaemia

shock (anaphylactic; life threatening), pruritic rash

myasthenia

grand mal convulsion, abnormal (unsteady) gait

petechiae, erythema multiforme (minor), erythema nodosum, fixed eruption

The most common Adverse Reactions based on spontaneous reports sorted by CIOMS III categories of frequency and COSTART (5th Edition, 1995) body system and terms calculated on patient exposure (n = 7790 reported cases, status 30.09.1997)

Incidence of frequency $< 0.01\%$

Digestive system:

liver necrosis (very rarely progressing to life-threatening hepatic failure), *life threatening* pseudomembranous colitis with possible fatal outcome

Haemic and lymphatic system:

petechiae (punctuate skin haemorrhages), pancytopenia (life-threatening), bone marrow, depression (life-threatening), agranulocytosis

Musculo-Skeletal system:

Tendinitis (predominantly achillotendinitis); partial or complete tendon rupture (predominantly achilles tendon)
Exacerbation of symptoms of myasthenia gravis.

Nervous system:

psychosis, intracranial hypertension, ataxia, hyperaesthesia, hypertonia, twitching

Skin and appendages:

Stevens-Johnson-Syndrome, epidermal necrolysis (Lyell-Syndrome)

Hypersensitivity:

Serum sickness like reaction

Special senses:

parosmia (impaired smell) anosmia (usually reversible on discontinuation)

Interactions

The simultaneous administration of APO-CIPROFLOXACIN and iron, sucralfate or antacids and highly buffered drugs (e.g. antiretrovirals), containing magnesium, aluminium, or calcium, reduce the absorption of ciprofloxacin.



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Consequently, APO-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.

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.

Concurrent administration of APO-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.

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.

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).

The simultaneous administration of APO-CIPROFLOXACIN and warfarin may intensify the action of warfarin

In particular cases, concurrent administration of APO-CIPROFLOXACIN and glibenclamide can intensify the action of glibenclamide (hypoglycaemia)

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and APO-CIPROFLOXACIN increases the ciprofloxacin serum concentrations.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of APO-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 APO-CIPROFLOXACIN therapy is indicated.

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Overdosage

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



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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.

Pharmaceutical Precautions

Store below 25°C. Protect from heat, light and moisture.
Shelf life: 24 months from the date of manufacture.

Medicine Classification

Prescription Medicine

Package Quantities

250mg: Blister packs of 10 and 30 tablets.

500mg: Blister packs of 10 and 30 tablets.

750mg: Blister packs of 10 and 30 tablets.

Further Information

APO-CIPROFLOXACIN tablets contain maize starch.

Preclinical 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	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



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Subacute 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:

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 Toxicity:

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



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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.



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Ciprofloxacin 250mg, 500mg and 750mg tablets

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.

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.

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