PACKAGE INSERT TEMPLATE FOR CIPROFLOXACIN TABLET

Brand or Product Name
[Product name] Tablet 250mg
[Product name] Tablet 500mg

Name and Strength of Active Substance(s)
Ciprofloxacin hydrochloride monohydrate ….mg equivalent to ciprofloxacin 250mg
Ciprofloxacin hydrochloride monohydrate ….mg equivalent to ciprofloxacin 500mg

Product Description
[Visual description of the appearance of the product (eg colour, markings etc)
eg : Tablet - White, circular flat beveled edge tablets marked '250' on one side

Pharmacodynamics
Ciprofloxacin is a synthetic broad spectrum quinolone antibacterial agent.

Mechanism of Action
Ciprofloxacin has in-vitro against virtually all 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 develops slowly through multiple-step mutations. Ciprofloxacin resistance due to spontaneous mutations occurs at a frequency of between $<10^{-9}$ to 10^{-6}. Cross-resistance among fluoroquinolones may occur when resistance arises through 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. Bacterial impermeability and/or expression of efflux pumps may impact ciprofloxacin susceptibility. Plasmid-mediated resistance encoded by the qnr gene has been reported. Resistance mechanisms that inactive penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines do 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 minimal 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.

Groupings of relevant species according to ciprofloxacin susceptibility:

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Bacillus anthracis
Aerobic Gram-negative micro-organisms
Aeromonas spp.
Brucella spp.
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi
Haemophilus influenzae
Legionella spp.
Moraxella catarrhalis
Neisseria meningitidis
Pasteurella spp.
Salmonella spp.
Shigella spp.
Vibrio spp.
Yersinia pestis
Anaerobic micro-organisms
Mobiluncus
Other micro-organisms
Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecalis
Staphylococcus spp.
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii
Burkholderia cepacia
Campylobacter spp.
Citrobacter freundii
Enterobacter aerogenes
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Morganella morganii
Neisseria gonorrhoeae
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Pseudomonas aeruginosa
Pseudomonas fluorescens
Serratia marcescens
Anaerobic micro-organisms
Peptostreptococcus spp.
Propionibacterium acnes

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*

Pharmacokinetics

Ciprofloxacin is suitable for oral and intravenous administration. Owing to its excellent antibacterial activity and its good pharmacokinetics properties, ciprofloxacin can be given orally for injections which previously could only be treated intravenously with, say, penicillins, cephalosporins or aminoglycosides.

For acute life-threatening infections or patients unable to take tablets it is advisable to commence treatment with the intravenous form of ciprofloxacin.

Following an initial intravenous dose (short-term 30-minute infusion), treatment can be continued with oral ciprofloxacin, which is a distinct advantage, especially from the patient's point of view.

Absorption and bioavailability

After oral administration ciprofloxacin is largely absorbed from the small intestine. A specific study with C14-labelled ciprofloxacin showed that 73% of the dose was absorbed intestinally. Absorption is rapid, leading to peak serum levels after 60-90 minutes.

Absolute bioavailability has been shown to be 70 – 80 % in various studies by a direct comparison between the oral and intravenous forms of ciprofloxacin.

Distribution volume

The distribution volume of ciprofloxacin in steady state is 2–3 litres/kg. This unusually high figure, more than 10 times that of beta-lactam antibiotics and aminoglycosides, is an indication that ciprofloxacin reaches higher concentrations in tissue and body fluids than in serum. Concentrations were in fact measured in a number of tissue and fluid samples that were several times higher than the corresponding serum levels.

Concentrations in body fluids and tissues/protein binding

The pharmacokinetics properties of ciprofloxacin suggest good tissue penetration, with distribution volume as a good indicator of the high tissue concentrations one may expect to find.

The rate of protein binding and degree of ionisation are decisive factors in the diffusion of a substance from the intra- to the extravascular space. It is reasonable to assume that only the proportion of the substance not bound to serum proteins and not ionized is able to diffuse into the extravascular space. Protein binding by ciprofloxacin is low (approx. 20 – 30%) and the substance is mostly found in a non-ionised form in the plasma. Therefore virtually the entire dose administered is free to diffuse into the extravascular space.

In addition, sub-cellular structures and certain physiological factors (e.g. pH in body fluids and tissues) may bring about a relative intracellular concentration of ciprofloxacin. This is how the concentrations in certain body fluids and tissues far surpass the corresponding serum levels.

Metabolism
Low concentrations of four metabolites have been reported, which were identified as:
Desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.
The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours. Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h. Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Indication
Consideration should be given to applicable official guidances on the appropriate use of antibacterial agents.

Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens:
- Infections of the respiratory tract
Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Branhamella, Legionella, and Staphylococcus.
- Infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis), especially if these are caused by gram negative organisms including *Pseudomonas aeruginosa* or by staphylococci.
- Infections of the eyes
- 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
- Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)
- Selective intestinal decontamination in immunosuppressed patients

Prophylaxis of invasive infections due to Neisseria meningitidis.
Children and adolescents
Ciprofloxacin may be used in children for the second- and third-line treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli* (age range applied in clinical studies: 1 – 17 years) and for the treatment of broncho-pulmonary infections of cystic fibrosis associated with *Pseudomonas aeruginosa* (age range applied in clinical studies: 5 – 17 years).

Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissues.
The clinical trials in children were performed in the indications listed above. For other indications clinical experience is limited.

Inhalational anthrax (post-exposure) in adults and in children:
To reduce the incidence or progression of disease following exposure to aerosolised Bacillus anthracis.

Recommended Dosage
Adults
Unless otherwise prescribed, the following guideline doses are recommended:

Indication	Recommended dosage (tablets)
Respiratory tract infection (according to severity and organism)	2 x 500 mg to 2 x 750mg
Urinary tract infections: -acute, uncomplicated -cystitis in women(before menopause) -complicated	 2 x 250 mg to 2 x 500 mg single dose 500 mg 2 x 500 mg to 2 x 750 mg
Gonorrhea -extragenital -acute, uncomplicated	 2 x 250 mg single dose 500 mg
Genital infections - uncomplicated gonorrhea (including extragenital sites of infection) - adnexitis, prostatitis, epididymo-orchitis	 1 x 500 mg 2 x 500 mg to 2 x 750 mg
Diarrhea	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 -Septicemia -Peritonitis In particular when Pseudomonas, Staphylococcus or Streptococcus is present	2 x 750 mg
Inhalational anthrax (post-exposure)	2x500mg
Prophylaxis of invasive infections due to Neisseria meningitides	1 x 500 mg as a single dose

Additional information on special patient population
Children and adolescents
- Cystic Fibrosis

Clinical and pharmacokinetic data support the use of Ciprofloxacin in pediatric cystic fibrosis patients (aged 5 – 17 years) with broncho-pulmonary infections associated with Pseudomonas aeruginosa infection, at a dose of 20 mg/kg body weight oral twice daily with a maximum of 750 mg per dose or 10 mg/kg body weight intravenous three times daily with a maximum of 400 mg per dose.

- Complicated Urinary Tract Infections and Pyelonephritis

For complicated urinary tract infections or pyelonephritis the dose is 10 mg/kg body weight oral twice daily to 20 mg/kg body weight oral twice daily with a maximum of 750 mg per dose or 6 mg/kg body weight intravenous three times daily to 10 mg/kg body weight intravenous three times daily with a maximum of 400 mg per dose.

Geriatric patients (> 65 years)

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

Patients with renal and hepatic impairment

Adults

- Impaired renal function

- Patients with creatinine clearance between 30 and 60 mL/min/1.73m2 (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 mL, the maximum daily dose should be 1000 mg for oral administration or 800 mg for an intravenous regimen
- Patients with creatinine clearance less than 30 mL/min/1.73m2 (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 mL, the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen

- Impaired renal function and hemodialysis

- Patients with creatinine clearance between 30 and 60 mL/min/1.73m2 (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 mL, the maximum daily dose should be 1000 mg for oral administration (all formulations) or 800 mg for an intravenous regimen
- Patients with creatinine clearance less than 30 mL/min/1.73m2 (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 mL, the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen on dialysis days after dialysis

- Impaired renal function and continuous ambulatory peritoneal dialysis (CAPD)

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

- Impaired liver function

- No dose adjustment is required

- Impaired renal and liver function

- Patients with creatinine clearance between 30 and 60 mL/min/1.73m2 (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 mL, the maximum daily dose should be 1000 mg for oral administration (all formulations) or 800 mg for an intravenous regimen.
- Patients with creatinine clearance less than 30 mL/min/1.73m2 (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 mL, the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen.

Children and adolescents

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

Inhalational Anthrax (Post-exposure) in Adults and Children
Adults
Oral administration: 500 mg ciprofloxacin twice daily (See table above).

Children and adolescents
Oral administration: 15 mg ciprofloxacin /kg body weight twice daily. The maximum of 500 mg per dose should not be exceeded (maximum daily dose of 1000 mg ciprofloxacin).
Administration of the medicinal product should begin as soon as possible after suspected or confirmed exposure.

Method of administration
Film-coated tablets
Oral use

- Ciprofloxacin film-coated tablets are to be swallowed whole with a small amount of fluid.

Ciprofloxacin film coated tablets can be taken independently of mealtimes.

If they are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, Ciprofloxacin film-coated 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 Ciprofloxacin film-coated tablets because of the severity of the illness or for other reasons (e.g. patients on enteral nutrition), 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 gonorrhea and cystitis
- up to 7 days for infections of the kidneys, urinary tract and abdominal cavity
- over the entire period of the neutropenic phase in patients with weakened body defenses
- a maximum of 2 months in osteomyelitis
- and 7 – 14 days in all other infections

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

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

Children and adolescents

- Cystic Fibrosis

For broncho-pulmonary infections of cystic fibrosis associated with Pseudomonas aeruginosa infection in pediatric patients (aged 5 – 17 years), the duration of treatment is 10 – 14 days.

- Complicated Urinary Tract Infections and Pyelonephritis

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

Inhalational Anthrax (Post-exposure) in Adults and Children
60 days from the confirmation of Bacillus anthracis exposure

Mode of Administration
Oral

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 the serum tizanidine concentrations associated with clinically relevant tizanidine-induced side effects (hypotension, somnolence, drowsiness) can occur.

Warnings and Precautions
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. 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.

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.

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 endangered because of possible central-nervous side effects.

In some instances the CNS reactions occurred after the first administration of Ciprofloxacin already. 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.

Hypersensitivity
In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and 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
At any sign of tendinitis (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 (as the risk for tendon rupture might increase otherwise). Tendon rupture (predominantly Achilles tendon) has been reported predominantly in the elderly or on prior systemic treatment with glucocorticoids. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to quinolone treatment.

[Specific package insert requirement for ciprofloxacin]
Exacerbation of myasthenia gravis
Fluroquinolones have neuromuscular blocking activity and may exacerbate muscle weakeness in person with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluroquionolones use in persons with myasthenia gravis. Avoid fluroquinolones in patients with known history of myasthenis gravis.

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 photosensitation (i.e. sunburn-like skin reactions) occurs.

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.

NaCl load for IV formulation
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.) the additional sodium load should be taken into account.

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 section "Undesirable 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 broncho-pulmonary infections of cystic fibrosis caused by *Pseudomonas aeruginosa* infection (children aged 5 – 17 years), complicated urinary tract infections and pyelonephritis due to *Escherichia 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.

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.

Effects on ability to drive and use machines
Even when the drug 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.

Interactions with Other Medicaments
Chelation Complex Formulation
The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), 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. The restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Food and Dairy Products
The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and 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 therefore be checked and the theophylline dose appropriately reduced.

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 control the serum creatinine concentrations in these patients frequently (twice a week).

Warfarin
The simultaneous administration of ciprofloxacin and warfarin may intensify the action of warfarin.

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

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

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.

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 Cmax 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 medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole of 60 and 84%, respectively. Although ropinirole treatment was well tolerated, case reports that a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

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-desmethylclozapnie were increased by 29% and 31%, respectively

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

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

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).

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 the benefits.

Statement on Usage During Pregnancy and Lactation
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 not entirely improbable that the drug could cause damage to articular cartilage in the immature organism. Animal studies have not shown any evidence of teratogenic effects (malformations).

Adverse Effects / Undesirable Effects

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, Anemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocytaemia	Haemolytic anaemia, Agranulocytosis, Pancytopenia (life-threatening), Bone marrow depression (life-threatening)	
Immune System Disorders				
		Allergic reaction, Allergic oedema /	Anaphylactic reaction,	

Common	Uncommon	Rare	Very rare	Not known
		angiooedema	Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and Nutrition Disorders				
	Anorexia	Hyperglycemia		
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 Dysaesthesia, Hypoaesthesia, Tremor, Seizures, Vertigo	Migraine, Disturbed coordination, Smell disorders, Hyperesthesia, Intracranial hyper-tension	Peripheral neuropathy and polyneuropathy
Eye Disorders				
		Visual disturbances	Visual color 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				
		Dyspnea (including asthmatic condition)		
Gastrointestinal Disorders				
Nausea Diarrhea	Vomiting, Gastrointestinal and abdominal pains, Dyspepsia, Flatulence		Pancreatitis	
Hepato-biliary Disorders				

Common	Uncommon	Rare	Very rare	Not known
	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 minor, 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				
Injection and infusion site reactions (only intravenous administration)	Unspecific pain, Feeling unwell, Fever	Oedema, Sweating (hyper-hidrosis)	Gait disturbance	
Investigations				
	Increase in blood alkaline phosphatase	Prothrombin level abnormal, Increased amylase		

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

Overdose and Treatment
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.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]