

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

QUINTOR

(Ciprofloxacin Hydrochloride 250mg and 500mg Tablets)

COMPOSITION

QUINTOR-250

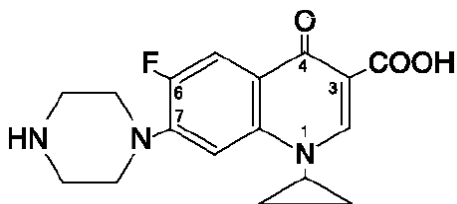
Each film coated tablet contains: Ciprofloxacin Hydrochloride I.P. equivalent to Ciprofloxacin 250mg
Colours: Tartrazine, Titanium Dioxide I.P.

QUINTOR-500

Each film coated tablet contains: Ciprofloxacin Hydrochloride I.P. equivalent to Ciprofloxacin 500mg
Colours: Tartrazine, Titanium Dioxide I.P.

DESCRIPTION

Ciprofloxacin is a synthetic broad-spectrum antimicrobial agent. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is:



CLINICAL PHARMACOLOGY

PHARMACODYNAMICS

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between

ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. 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 *qnr*-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations:

Organism	Susceptible	Resistant
<i>Enterobacteriaceae</i>	≤ 0.5 mg/L	> 1.0 mg / L
<i>Pseudomonas spp.</i>	≤ 0.5 mg /L	>1.0 mg /L
<i>Acinetobacter spp.</i>	≤ 1.0 mg / L	> 1.0 mg / L
<i>Staphylococcus spp.</i> ¹	≤ 1.0 mg / L	> 1.0 mg / L
<i>Streptococcus pneumoniae</i> ²	≤ 0.25 mg/L	> 2.0 mg / L
<i>H.influenzae</i> and <i>M.catarrhalis</i> ³	≤ 0.5 mg / L	> 0.5 mg / L
<i>Non-species related breakpoints</i> ⁴	≤ 0.5 mg / L	> 1.0 mg / L

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

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see section 4.4)

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, *Enterococcus faecium*, *Listeria monocytogenes*, *Aerobic Gram-negative micro-organisms*, *Stenotrophomonas maltophilia*,

Anaerobic micro-organisms

Excepted as listed above

Other micro-organisms

Mycoplasma genitalium, *Ureaplasma urealyticum*

PHARMACOKINETICS

QUINTOR INFUSION

Absorption

When ciprofloxacin was administered as an i.v. infusion, the mean plasma peak concentrations were reached at the end of infusion. The pharmacokinetics of ciprofloxacin was linear within the dose range studied, i.e. up to an i.v. dose of 400 mg (infusion time 60 min).

Elimination half-life in serum after both oral and intravenous administration is 4-6 hours in patients with normal renal function. Total clearance after i.v. administration is about 35 l/h. No accumulation of ciprofloxacin or its metabolites was seen after daily administration of two or three i.v. doses.

Pharmacokinetic analyses showed that the AUCs were similar when ciprofloxacin was given as i.v. doses of 200 mg over 60 minutes at 12-hour intervals compared to oral doses of 250 mg at 12-hour intervals.

The AUCs were also similar when ciprofloxacin was given as 400 mg i.v. doses over 60 minutes at 12-hour intervals and as oral doses of 500 mg at 12-hour intervals. The peak plasma concentrations (C_{max}) were equally high when i.v. doses of 400 mg were given over 60 minutes at 12-hour intervals or oral doses of 750 mg were given at 12-hour intervals. The AUCs were equal when ciprofloxacin was given as i.v. doses of 400 mg over 60 minutes at 8-hour intervals or as oral doses of 750 mg at 12-hour intervals.

Only 20-30 % of ciprofloxacin binds to plasma proteins, and it is mostly present in plasma in an unionised form. Due to this, ciprofloxacin is widely diffused in the extravascular space, and its concentrations in inflamed areas (e.g. tissues) are higher than in serum. Distribution volume in steady state is 2-3 l/kg.

Pharmacokinetics in children

In a clinical pharmaceutical trial where ten children aged 6-16 years were administered 10 mg/kg ciprofloxacin intravenously over 30 minutes at 12-hour intervals, the mean peak plasma concentration was 8.3 µg/ml and the corresponding minimum plasma concentration ranged within 0.09-0.26 µg/ml.

After the second i.v. dose, the patients began to take an oral dose of 15 mg/kg at 12-hour intervals, and this resulted in a mean peak concentration of 3.6 µg/ml after the first oral dose. Safety data on long-term use in children, including the effects of the drug on cartilage, are limited.

Metabolism and excretion

Ciprofloxacin is mostly excreted unchanged through the kidneys into urine. After an oral dose, about 55% of ciprofloxacin is eliminated in urine, the corresponding percentage after a parenteral dose being approximately 70%. Renal clearance is 0.18-0.3 l/h/kg and total serum

clearance is 0.48-0.60 l/h/kg. Renal excretion of ciprofloxacin takes place through both glomerular filtration and tubular secretion.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral and after intravenous administration.

Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renal function must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

Ciprofloxacin undergoes some metabolism into desethylene ciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 and M3 have antimicrobial properties similar to or weaker than that of nalidixine acid.

The antimicrobial efficacy of M4, which is present in smaller quantities, corresponds to that of norfloxacin.

Pharmacokinetic studies on children with cystic fibrosis have shown that the recommended doses of 20 mg/kg twice a day orally or 10 mg/kg three times a day intravenously result in similar plasma concentration as a function of time as the currently recommended doses of adults

QUINTOR TABLET

Absorption

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later.

Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70-80%.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a nonionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides

blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). 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.

Excretion of ciprofloxacin (% of dose)		
	<i>Oral Administration</i>	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M ₁ -M ₄)	11.3	7.5

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.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4

mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

PRECLINICAL SAFETY DATA

Renal damage was observed in animal experiments only at high doses and in association with crystalluria. Renal damage without crystalluria was not seen in animal experiments and is not considered to be a primary toxic effect, but a typical secondary inflammatory foreign body reaction to the precipitation of a crystal-like complex of ciprofloxacin, magnesium and proteins.

Similar to other gyrase inhibitors, ciprofloxacin may induce damage to the large, bearing joints during the growth phase of juvenile animals.

Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of Ciprofloxacin in vitro and in animal experiments in comparison with other fluoroquinolones.

Ciprofloxacin showed positive results in two in vitro gene toxicity studies (mouse lymphoma cell forward mutation assay and rat hepatocyte DNA repair assay).

Other preclinical effects were observed only at exposures sufficiently in excess of the maximum human exposure that concern for human safety is negligible with regard to the animal data.

Articular tolerability

As reported for 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 caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

INDICATIONS AND USAGE

Quintor infusion is indicated in the treatment of acute respiratory tract infections, acute urinary tract infections, acute skin and soft tissue infections, severe systemic infections such

as septicemia, bacteremia and acute infections in immunocompromised host. Severe surgical infections such as intra-abdominal abscess, acute peritonitis, cholangitis and acute cholecystitis, severe pelvic infection, acute gastrointestinal tract infections, acute osteomyelitis and severe sexually transmitted disease such as gonorrhoea.

Quintor Tablet is indicated for Respiratory Tract Infections: Acute bronchitis, acute exacerbation of cystic fibrosis, emphysema, lung abscess, infected bronchiectasis, pneumonia, sinusitis and mastoiditis. Urinary Tract Infections: Acute pyelonephritis, complicated urinary tract infections, recurrent UTI and Infections caused by multi-drug resistant organisms. Skin and Soft Tissue Infections: Infected wounds and postoperative infections caused by Gram-negative organisms e.g.. *Enterobacteriaceae*, *Ps. aeruginosa* and resistant *staphylococcal* Infections. Severe Systemic Infections: Septicemia, bacteremia and infections In Immunocompromised host. Surgical Infections: Intra-abdominal abscess, peritonitis, cholangitis and cholecystitis. Gynecological Infections: Severe pelvic Infections caused by susceptible organisms. Gastrointestinal Tract Infections: Typhoid fever, Including carrier stage and resistant *Salmonella typhi* Infections. Bone and Joint Infections: Since adequate levels of ciprofloxacin are achieved in bone It Is useful for treatment of acute and chronic osteomyelitis. Sexually Transmitted Disease: Uncomplicated Gonococcal infections including those caused by beta-lactamase resistant strains and chancroid caused by *H. ducreyi*.

CONTRAINDICATIONS

Ciprofloxacin is contraindicated in:

- Patients with a hypersensitivity to ciprofloxacin, quinoline carboxylic acid derivatives or to any of the excipients
- Pregnancy and lactation
- Patients with a history of tendon disorder related to fluoroquinolone administration
- Concurrent administration of ciprofloxacin and tizanidine
- Children and adolescents - except for the treatment of acute pulmonary exacerbation of cystic fibrosis caused by *Pseudomonas aeruginosa* in children aged 5 to 17 years

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients

usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants.

Fluoroquinolones, including ciprofloxacin, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid ciprofloxacin in patients with known history of myasthenia gravis

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

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

Streptococcal Infections (including Streptococcus pneumoniae)

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

Genital tract infections

Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections

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

Travellers' diarrhoea

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

Infections of the bones and joints

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

Inhalational anthrax

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

Children and adolescents

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

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals.

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

Broncho-pulmonary infections in cystic fibrosis

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

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.

Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

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

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

Hypersensitivity

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

Musculoskeletal System

Ciprofloxacin should generally not be used in patients with a history of tendon

disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids.

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.

Ciprofloxacin should be used with caution in patients with myasthenia gravis.

Photosensitivity

Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

Central Nervous System

Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders, which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued. Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin.

Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition.

Cardiac disorders

Since ciprofloxacin is associated with cases of QT prolongation, caution should be exercised when treating patients at risk for torsades de pointes arrhythmia.

Gastrointestinal System

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment. In such cases, ciprofloxacin should

immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system

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

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.

Glucose-6-phosphate dehydrogenase deficiency

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

Resistance

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

Cytochrome P450

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

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended.

Interaction with tests

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

Injection Site Reaction

Local intravenous 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

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

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Effects of other products on ciprofloxacin:

Chelation Complex Formation

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 reduces 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 H₂ receptor blockers.

Food and Dairy Products

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

Probenecid

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

Effects of ciprofloxacin on other medicinal products:

Tizanidine

Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is

associated with a potentiated hypotensive and sedative effect.

Methotrexate

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

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.

Other xanthine derivatives

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

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole

It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and

31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised

PREGNANCY AND LACTATION

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

ADVERSE EXPERIENCES

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	Frequency not known
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with		

			possible fatal outcome)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytæmia	Haemolytic anaemia Agranulocytosis Pancytopenia (lifethreatening) Bone marrow depression (lifethreatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (lifethreatening) Serum sickness like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures Vertigo	Migraine Disturbed coordination Gait Disturbance Olfactory nerve disorders	Peripheral Neuropathy

				Intracranial hypertension	
Eye Disorders			Visual disturbances	Visual colour Distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, 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 Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin and Subcutaneous		Rash Pruritus	Photosensitivity reactions	Petechiae Erythema	

Tissue Disorders		Urticaria		multiforme Erythema nodosum Stevens- Johnson syndrome (potentially lifethreatening) Toxic epidermal necrosis (potentially lifethreatening)	
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) worsening of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Asthenia Fever	Oedema Sweating (hyperhidrosis)		

Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		
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These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation.

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

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

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

OVERDOSAGE

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

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

Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated.

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

dialysis.

DOSAGE AND ADMINISTRATION

QUINTOR INFUSION

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications		Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Infections of the lower respiratory tract		400 mg twice daily to 400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days

	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including <i>Shigella</i> spp. other than <i>Shigella dysenteriae</i> type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by <i>Shigella dysenteriae</i> type 1	400 mg twice daily	5 days
	Diarrhoea caused by <i>Vibrio cholerae</i>	400 mg twice daily	3 days

	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
	Infections of the skin and soft tissue	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Bone and joint infections	400 mg twice daily to 400 mg three times a day	max. of 3 months
	Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.	400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
	Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	400 mg twice daily	60 days from the confirmation of <i>Bacillus anthracis</i> exposure

Children and adolescents

Indication	Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days

Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of <i>Bacillus anthracis</i> exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [μmol/L]	Intravenous Dose [mg]
> 60	< 124	See Usual Dosage.
30 - 60	124 to 168	200 - 400 mg every 12 h
< 30	> 169	200 - 400 mg every 24 h

Patients on haemodialysis	> 169	200 - 400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200 - 400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

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

Method of administration

Ciprofloxacin solution for infusion should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.

In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin solution for infusion and 30 minutes for 200 mg Ciprofloxacin solution for infusion. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.

The infusion solution can be infused either directly or after mixing with other compatible infusion solutions

QUINTOR TABLET

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults

Indications	Daily dose in mg	Total duration of treatment (potentially including initial
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			parenteral treatment with ciprofloxacin)
Infections of the lower respiratory tract		500 mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Malignant external otitis	750 mg twice daily	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250 mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)

	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal urethritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intraabdominal infections	Diarrhoea caused by bacterial pathogens including <i>Shigella</i> spp. other than <i>Shigella dysenteriae</i> type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day
	Diarrhoea caused by <i>Shigella dysenteriae</i> type 1	500 mg twice daily	5 days
	Diarrhoea caused by <i>Vibrio cholerae</i>	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500 mg twice	7 to 14 days

	daily to 750 mg twice daily	
Bone and joint infections	500 mg twice daily to 750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.	500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to <i>Neisseria meningitidis</i>	500 mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	500 mg twice daily	60 days from the confirmation of <i>Bacillus anthracis</i> exposure

Children and adolescents

Indications	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	10 to 14 days
Complicated urinary tract	10 mg/kg body weight twice	10 to 21 days

infections and pyelonephritis	daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose.	60 days from the confirmation of <i>Bacillus anthracis</i> exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [μmol/L]	Oral Dose [mg]
> 60	< 124	
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

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

Method of administration

Tablets are to be swallowed unchewed with fluid. They can be taken independent of mealtimes. If taken on an empty stomach, the active substance is absorbed more rapidly.

Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice)

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

Expiry date

Do not use later than the date of expiry.

Storage

KEEP IN A COOL DRY PLACE, PROTECTED FROM LIGHT

Presentation

QUINTOR-250, QUINTOR-500 is available in Blister of 10 Tablets

MARKETED BY:



TORRENT PHARMACEUTICALS LTD.

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