

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

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**QUINTOR INFUSION**  
**(Ciprofloxacin Injection U.S.P., 200 mg/100 ml)**

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**COMPOSITION**

Ciprofloxacin Injection U.S.P. 200 mg/100 ml

**INDICATION**

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.

**DOSE AND METHOD OF ADMINISTRATION**

The dosage of Quintor is determined by the severity and type of infections, the sensitivity of the causative organisms and the age, and renal function of the patient. Quintor is compatible with all i.v. fluids. Quintor may be administered by short term infusion over a period of 30-60 minutes. The solution should not be used if it is found discoloured or if it contains any suspended particles.

The usual recommended dosage of Quintor in acute urinary tract infections is 100mg twice daily by slow i.v. infusion. In acute respiratory tract infections, Quintor infusion is given in dose of 200mg twice daily by slow i.v. infusion. In gonorrhoea, single dose of 100mg i.v. is sufficient. In majority of other infections, 200mg Quintor should be administered by slow i.v. infusion every 12 hours daily. In patients with severe renal impairment (Creatinine clearance less than 20ml/min) the total daily dose of Quintor infusion should be reduced to half of the usual recommended dose. The usual treatment period of acute infections is 5 to 7 days with Quintor infusion. Initial i.v. administration may be followed by treatment with oral Quintor whenever necessary.

**CONTRAINDICATIONS**

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients
- Concomitant administration of ciprofloxacin and tizanidine

**SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

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* isolates.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If

clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

#### Urinary tract infections

Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

#### 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.

#### Paediatric population

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, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. 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, because symptoms can be exacerbated.

### Vision disorders

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

### 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

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. 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 first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such 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

Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:

- congenital long QT syndrome
- concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.

### Hypoglycemia

As with other quinolones, hypoglycemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended.

### 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.

### Impaired renal function

Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

### 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, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). 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. Co-administration of ciprofloxacin and tizanidine is contra-indicated.

### 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.

## **DRUG INTERACTION**

Effects of other products on ciprofloxacin:

### Drugs known to prolong QT interval

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)

### 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. 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.

### Cyclosporin

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

### Vitamin K antagonists

Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant 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 normalised 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).

### Duloxetine

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

### Ropinirole

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.

### Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products 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 with clozapine for 7 days, serum concentrations of clozapine and N-desmethyl clozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.

### Sildenafil

$C_{max}$  and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

### Agomelatine

In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration.

### Zolpidem

Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

## **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.

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

### Breast-feeding

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.

## UNDESIRABLE EFFECTS

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

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.

<b>System Organ Class</b>	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	<b>Frequency not known</b> (cannot be estimated from the available data)
<b>Infections and Infestations</b>		Mycotic super-infections			
<b>Blood and Lymphatic System Disorders</b>		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytopenia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
<b>Immune System Disorders</b>			Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
<b>Metabolism and Nutrition Disorders</b>		Decreased appetite	Hyperglycaemia Hypoglycaemia		
<b>Psychiatric Disorders</b>		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal	Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and	Mania, incl. hypomania

			ideations/though ts or suicide attempts and completed suicide) Hallucinations	completed suicide)	
<b>Nervous System Disorders</b>		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy
<b>Eye Disorders</b>			Visual disturbances (e.g. diplopia)	Visual colour distortions	
<b>Ear and Labyrinth Disorders</b>			Tinnitus Hearing loss / Hearing impaired		
<b>Cardiac Disorders</b>			Tachycardia		Ventricular arrhythmia, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged
<b>Vascular Disorders</b>			Vasodilatation Hypotension Syncope	Vasculitis	
<b>Respiratory, Thoracic and Mediastinal Disorders</b>			Dyspnoea (including asthmatic condition)		
<b>Gastrointestinal Disorders</b>	Nausea Diarrhoea	Vomiting	Antibiotic associated colitis	Pancreatitis	



		Gastrointestinal and abdominal pains Dyspepsia Flatulence	(very rarely with possible fatal outcome)		
<b>Hepatobiliary Disorders</b>		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
<b>Skin and Subcutaneous Tissue Disorders</b>		Rash Pruritus Urticaria	Photosensitivity reactions	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute Generalised Exanthematous Pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
<b>Musculoskeletal and Connective Tissue Disorders</b>		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) Exacerbation of symptoms of myasthenia gravis	
<b>Renal and Urinary Disorders</b>		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		

<b>General Disorders and Administration Site Conditions</b>	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
<b>Investigations</b>		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

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, Thrombocytopenia, 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 population

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

### **OVERDOSE**

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, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.

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

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

### **PHARMACOLOGICAL PROPERTIES**

#### **Pharmacodynamic properties**

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.

#### Pharmacokinetic/pharmacodynamic 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

Microorganisms	Susceptible	Resistant
<i>Enterobacteriaceae</i>	S ≤ 0.5 mg/L	R > 1 mg/L
<i>Pseudomonas</i> spp.	S ≤ 0.5 mg/L	R > 1 mg/L
<i>Acinetobacter</i> spp.	S ≤ 1 mg/L	R > 1 mg/L
<i>Staphylococcus</i> spp. <sup>1</sup>	S ≤ 1 mg/L	R > 1 mg/L
<i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i>	S ≤ 0.5 mg/L	R > 0.5 mg/L
<i>Neisseria gonorrhoeae</i>	S ≤ 0.03 mg/L	R > 0.06 mg/L
<i>Neisseria meningitidis</i>	S ≤ 0.03 mg/L	R > 0.06 mg/L
Non-species-related breakpoints*	S ≤ 0.5 mg/L	R > 1 mg/L

<sup>1</sup> *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

\* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

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).

<b>COMMONLY SUSCEPTIBLE SPECIES</b>
<u>Aerobic Gram-positive micro-organisms</u> <i>Bacillus anthracis</i> (1)
<u>Aerobic Gram-negative micro-organisms</u> <i>Aeromonas</i> spp. <i>Brucella</i> spp. <i>Citrobacter koseri</i> <i>Francisella tularensis</i> <i>Haemophilus ducreyi</i> <i>Haemophilus influenzae</i> * <i>Legionella</i> spp. <i>Moraxella catarrhalis</i> * <i>Neisseria meningitidis</i> <i>Pasteurella</i> spp. <i>Salmonella</i> spp.* <i>Shigella</i> spp.* <i>Vibrio</i> spp. <i>Yersinia pestis</i>
<u>Anaerobic micro-organisms</u> <i>Mobiluncus</i>
<u>Other micro-organisms</u> <i>Chlamydia trachomatis</i> (\$) <i>Chlamydia pneumoniae</i> (\$) <i>Mycoplasma hominis</i> (\$) <i>Mycoplasma pneumoniae</i> (\$)
<b>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</b>
<u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> (\$) <i>Staphylococcus</i> spp. *(2)
<u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> <sup>+</sup> <i>Burkholderia cepacia</i> <sup>+</sup> * <i>Campylobacter</i> spp. <sup>+</sup> * <i>Citrobacter freundii</i> * <i>Enterobacter aerogenes</i> <i>Enterobacter cloacae</i> * <i>Escherichia coli</i> * <i>Klebsiella oxytoca</i> <i>Klebsiella pneumoniae</i> * <i>Morganella morganii</i> * <i>Neisseria gonorrhoeae</i> * <i>Proteus mirabilis</i> * <i>Proteus vulgaris</i> * <i>Providencia</i> spp. <i>Pseudomonas aeruginosa</i> * <i>Pseudomonas fluorescens</i> <i>Serratia marcescens</i> *
<u>Anaerobic micro-organisms</u>

<i>Peptostreptococcus</i> spp. <i>Propionibacterium acne</i>
<b>INHERENTLY RESISTANT ORGANISMS</b>
<u>Aerobic Gram-positive micro-organisms</u> <i>Actinomyces</i> <i>Enterococcus faecium</i> <i>Listeria monocytogenes</i>
<u>Aerobic Gram-negative micro-organisms</u> <i>Stenotrophomonas maltophilia</i>
<u>Anaerobic micro-organisms</u> Excepted as listed above
<u>Other micro-organisms</u> <i>Mycoplasma genitalium</i> <i>Ureaplasma urealiticum</i>
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate $\geq 50\%$ in one or more EU countries (\$): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of <i>Bacillus anthracis</i> spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on <i>in-vitro</i> susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant <i>S. aureus</i> very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

## Pharmacokinetic properties

### Absorption

Following an intravenous infusion of ciprofloxacin, the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a  $C_{max}$  similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

### Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised 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.

### Biotransformation

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.

	<b>Excretion of ciprofloxacin (% of dose)</b>	
	<b>Intravenous Administration</b>	
	<b>Urine</b>	<b>Faeces</b>
Ciprofloxacin	61.5	15.2
Metabolites (M <sub>1</sub> -M <sub>4</sub> )	9.5	2.6

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**

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

### 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.

### **EXPIRY DATE**

Do not use later than the date of expiry.

### **STORAGE:**

Store below 30° C, protect from light. Do not freeze.

### **PRESENTATION:**

Quintor infusion is supplied in bottle of 100ml, each ml containing ciprofloxacin lactate equivalent to ciprofloxacin 2mg.

### **MARKETED BY**



TORRENT PHARMACEUTICALS LTD.

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**IN/QUINTOR INFUSION 200 mg/100 ml/SEP-16/01/PI**