# SUMMARY OF PRODUCT CHARACTERISTICS

## NAME OF THE MEDICINAL PRODUCT

## <TRADE NAME> <STRENGTH> Solution for infusion.

## <REGARDING THE APPROVAL>

1. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 ml of solution for infusion contains

<STRENGTH> <GENERIC NAME>

Excipients with known effect:

<REGARDING THE APPROVAL>

For the full list of excipients, see section 6.1.

1. **PHARMACEUTICAL FORM**

Solution for infusion.

<REGARDING THE APPROVAL>

1. **CLINICAL PARTICULARS**
   1. **Therapeutic indications**

<GENERIC NAME> <STRENGTH> Solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to <GENERIC NAME> before commencing therapy.

Adults

* Lower respiratory tract infections due to Gram-negative bacteria
* Exacerbations of chronic obstructive pulmonary disease

In exacerbation of chronic obstructive pulmonary disease <GENERIC NAME> 2 mg/ml Solution for infusion should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections

* Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis pneumonia
* Chronic suppurative otitis media
* Acute exacerbation of chronic sinusitis especially if these are caused by Gram negative bacteria
* Acute pyelonephritis
* Bacterial prostatitis
* Genital tract infections
* Epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae pelvic inflammatory disease including cases due to susceptible Neisseria gonorrhoeae
* Infections of the gastro-intestinal tract (e.g.travellers` diarrhoea)
* Intra-abdominal infections
* Infections of the skin and soft tissue caused by Gram-negative bacteria
* Malignant external otitis
* Infections of the bones and joints
* Inhalation anthrax (post-exposure prophylaxis and curative treatment)

<GENERIC NAME> may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Children and adolescents

* Broncho-pulmonary infections due to *Pseudomonas aeruginosa* in patients with cystic fibrosis
* Complicated urinary tract infections and acute pyelonephritis
* Inhalation anthrax (post-exposure prophylaxis and curative treatment)

<GENERIC NAME> may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of

antibacterial agents

* 1. **Posology and method of administration**

Posology

The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to <GENERIC NAME> 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 <GENERIC NAME> 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 <GENERIC NAME> 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  (see section  4.4) | Complicated pyelonephritis | 500 mg twice daily to  750 mg two times a day | Minimum 10 days. Ιt can be continued for longer than 21 days in some specific circumstances (such as abscesses) |
| Complicated cystitis and uncomplicated pyelonephritis | 500 mg twice a day | 7 days |
| Uncomplicated acute  cystitis | 250 mg twice a day to  500 mg two times a day | 3 days |
| For preclimateric women, 500 mg can be given as single dose | |
| Prostatitis | 500 mg twice daily to  750 mg two times a day | From 2 to 4 weeks (acute) to 4 to 6 weeks (chronic) |
| 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 gastrointestinal tract and intraabdominal infections | Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers’ diarrhoea | 400 mg twice daily | 1 day |
| Diarrhoea caused by *Shigella dysenteriae* type 1 | 400 mg twice daily | 5 days |
| Diarrhoea caused by  *Vibrio cholerae* | 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 |
| Neutropenic patients with fever that is suspected to be due to a bacterial infection, | | 400 mg twice daily to  400 mg three times a day | Therapy should be continued over the entire period of neutropenia |
| <GENERIC NAME> should be  coadministered with appropriate antibacterial agent(s) in accordance to official guidance. | | | |
| 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 *Bacillus anthracis* exposure |

Paediatric population

|  |  |  |
| --- | --- | --- |
| **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 acute 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 *Bacillus anthracis* 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 |

Elderly patients

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

Patient with renal and hepatic impairment

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

|  |  |  |
| --- | --- | --- |
| **Creatinine Clearance**  **[mL/min/1.73 m²]** | **Serum Creatinine [**μ**mol/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

<GENERIC NAME> 2 mg/ml Solution for infusion should be checked visually prior to use. It must not be used if cloudy.

<GENERIC NAME> 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 <GENERIC NAME> 2 mg/ml Solution for infusion. and 30 minutes for 200 mg <GENERIC NAME> 2 mg/ml 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 (see section 6.6).

#### Contraindications

* Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to other quinolones.
* Concomitant administration of <GENERIC NAME> and tizanidine (see section 4.5).

## Special warnings and precautions for use

## The use of <GENERIC NAME> should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with <GENERIC NAME> should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

## Aortic aneurysm and dissection, and heart valve regurgitation/incompetence

## Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.8).

## Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease or congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection or heart valve disease, or in presence of other risk factors or conditions predisposing

* for both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e.g. connective tissue disorders such as Marfan syndrome or, Ehlers-Danlos syndrome, , Turner syndrome, Behcet’s disease, hypertension, rheumatoid arthritis) or additionally
* for aortic aneurysm and dissection (e.g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren’s syndrome) or additionally
* for heart valve regurgitation/incompetence (e.g. infective endocarditis).The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. <GENERIC NAME> should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

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

<GENERIC NAME> monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections <GENERIC NAME> must be coadministered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)

<GENERIC NAME> 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 <GENERIC NAME> should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless <GENERIC NAME>-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 <GENERIC NAME> in the treatment of post-surgical intraabdominal infections.

Travellers’ diarrhoea

The choice of <GENERIC NAME> should take into account information on resistance to <GENERIC NAME> in relevant pathogens in the countries visited.

Infections of the bones and joints

<GENERIC NAME> 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 <GENERIC NAME> in children and adolescents should follow available official guidance.

<GENERIC NAME> 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 acute pyelonephritis

<GENERIC NAME> 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 <GENERIC NAME> use.

The use of <GENERIC NAME> 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 (see section 4.8) and may be life-threatening. If such reaction occurs, <GENERIC NAME> should be discontinued and an adequate medical treatment is required.

Musculoskeletal System

<GENERIC NAME> 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, <GENERIC NAME> 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 <GENERIC NAME>.

<GENERIC NAME> should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated (see section 4.8).

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with <GENERIC NAME> treatment should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Vision disorders

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

Photosensitivity

<GENERIC NAME> has been shown to cause photosensitivity reactions. Patients taking <GENERIC NAME> should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System

<GENERIC NAME> like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. <GENERIC NAME> should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur <GENERIC NAME> should be discontinued (see section 4.8). Psychiatric reactions may occur even after first administration of <GENERIC NAME>. 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, <GENERIC NAME> should be discontinued.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with <GENERIC NAME> should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see section 4.8).

Cardiac disorders

Caution should be taken when using fluoroquinolones, including <GENERIC NAME>, 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
* antiarrhythmics, 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 <GENERIC NAME>, in these populations (See section 4.2 Elderly patients, section 4.5, section 4.8, section 4.9).

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 (see section 4.8).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In 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 (see section 4.8). In such cases, <GENERIC NAME> 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 <GENERIC NAME> has been reported (see section 4.8). Patients receiving <GENERIC NAME> should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

Since <GENERIC NAME> is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of <GENERIC NAME>.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with <GENERIC NAME> (see section 4.8). 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 <GENERIC NAME> in patients with glucose-6-phosphate dehydrogenase deficiency. <GENERIC NAME> 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 <GENERIC NAME> bacteria that demonstrate resistance to <GENERIC NAME> may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for <GENERIC NAME>-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450

<GENERIC NAME> 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). Co-administration of <GENERIC NAME> and tizanidine is contraindicated. Therefore, patients taking these substances concomitantly with <GENERIC NAME> should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

The concomitant use of <GENERIC NAME> with methotrexate is not recommended (see section 4.5).

Interaction with tests

The *in-vitro* activity of <GENERIC NAME> against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking <GENERIC NAME>.

Injection Site Reaction

Local intravenous site reactions have been reported with the intravenous administration of <GENERIC NAME>. 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.

Sodium

This medicinal product contains <REGARDING THE APPROVAL> sodium per dose, equivalent to 35.39% of the WHO recommended daily intake for sodium for adults.

The maximum daily dose of this product is equivalent to 106.16 % of the WHO recommended maximum daily intake for sodium for adults.

Appropriate consideration should be taken when administering this product to children.

<GENERIC NAME> is considered high in sodium. This should be particularly taken into account for those on a low sodium diet.

* 1. **Interaction with other medicinal products and other forms of interaction** Effects of other products on ciprofloxacin*:*

Drugs known to prolong QT interval

<GENERIC NAME>, 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) (see section 4.4).

Probenecid

Probenecid interferes with renal secretion of <GENERIC NAME>. Co-administration of probenecid and <GENERIC NAME> increases <GENERIC NAME> 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 (Cmax 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 (see section 4.4).

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 (see section 4.4).

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 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 normalised ratio) is difficult to assess. The INR should be monitored frequently during and shortly after coadministration 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 Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration (see section 4.4).

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 Cmax 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).

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-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 (see section 4.4).

Sildenafil

Cmax 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.

* 1. **Fertility, pregnancy and lactation**

Pregnancy

The data that are available on administration of <GENERIC NAME> to pregnant women indicates no malformative or feto/neonatal toxicity of <GENERIC NAME>. 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 <GENERIC NAME> during pregnancy.

Breast-feeding

<GENERIC NAME> is excreted in breast milk. Due to the potential risk of articular damage, <GENERIC NAME> should not be used during breast-feeding.

* 1. **Effects on ability to drive and use machines**

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

* 1. **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 <GENERIC NAME> (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 <GENERIC NAME>.

| **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 superinfectio ns | Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4) |  |  |
| **Blood and**  **Lymphatic**  **System**  **Disorders** |  | Eosinophilia | Leukopenia  Anaemia  Neutropenia  Leukocytosis Thrombocytopeni a  Thrombocytaemi a | Haemolytic anaemia  Agranulocytosis  Pancytopenia  (life-threatening)  Bone marrow  depression  (lifethreatening) |  |
| **Immune**  **System**  **Disorders** |  |  | Allergic reaction Allergic oedema / angiooedema | Anaphylactic reaction Anaphylactic shock  (lifethreatening)  (see section 4.4) Serum  sicknesslike reaction |  |
| **Metabolism and Nutrition Disorders** |  | Decreased appetite | Hyperglycaemia  Hypoglycaemia  (see section 4.4) |  | Hypoglycaemic  Coma (see  section 4.4) |
| **Endocrine**  **Disorders** |  |  |  |  | Syndrome of inappropriat of e secretion antidiuretic hormone (SIADH) |
| **Psychiatric**  **Disorders\*** |  | Psychomotor hyperactivity  /agitation | Confusion and disorientation  Anxiety reaction  Abnormal dreams  Depression (potentially culminating in suicidal ideations/thought s or suicide attempts and completed suicide) (see section 4.4)  Hallucinations | Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts  and completed suicide)  (see section 4.4) |  |
| **Nervous**  **System**  **Disorders\*** |  | Headache  Dizziness Sleep disorders Taste disorders | Par- and  Dysaesthesia  Hypoaesthesia  Tremor  Seizures  (including  status epilepticus see section 4.4)  Vertigo | Disturbance Gait disturbance Olfactory nerve disorders  Intracranial  Hypertension and pseudotumor cerebri  Migraine coordination | Peripheral neuropathy and polyneuropath y  (see section  4.4) |
| **Eye**  **Disorders\*** |  |  | Visual  Disturbances  (e.g. diplopia) | Visual colour distortions |  |
| **Ear and**  **Labyrinth**  **Disorders\*** |  |  | Tinnitus  Hearing loss /  Hearing impaired |  |  |
| **Cardiac**  **Disorders\*\*** |  |  | Tachycardia |  | Ventricular arrhythmia, torsades de pointes (reported predominantly in patients with risk factors for  QT  prolongation),  ECG QT  prolonged (see sections 4.4 and  4.9). |
| **Vascular**  **Disorders\*\*** |  |  | Vasodilatation  Hypotension  Syncope | Vasculitis |  |
| **Respiratory,**  **Thoracic and**  **Mediastinal**  **Disorders** |  |  | Dyspnoea (including asthmatic condition) |  |  |
| **Gastrointesti nal Disorders** | Nausea  Diarrhoea | Vomiting  Gastrointesti nal and abdominal pains Dyspepsia Flatulence |  | Pancreatitis |  |
| **Hepatobiliary**  **Disorders** |  | Increase in transaminase s  Increased bilirubin | Hepatic impairment Cholestatic icterus Hepatitis | Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4) |  |
| **Skin and**  **Subcutaneous**  **Tissue**  **Disorders** |  | Rash  Pruritus  Urticaria | Photosensitivity reactions (see section 4.4) | Petechiae Erythema multiforme Erythema nodosum  Stevens- Johnson syndrome  (potentially lifethreatening) Toxic epidermal necrolysis (potentially lifethreatening) | Acute generalised exanthematous pustulosis  (AGEP), Drug reaction with eosinophilia and systemic symptoms (DRESS) |
| **Musculoskele tal and**  **Connective**  **Tissue**  **Disorders\*** |  | Musculoskele tal 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)  (see section 4.4)  Exacerbation of symptoms of myasthenia gravis (see section 4.4) |  |
| **Renal and**  **Urinary Disorders** |  | Renal impairment | Renal failure  Haematuria  Crystalluria (see section 4.4) Tubulointerstitial nephritis |  |  |
| **General Disorders and**  **Administratio n**  **Site**  **Conditions\*** | Injection and infusion site reactions (only intravenous administrat ion) | Asthenia  Fever | Oedema  Sweating  (hyperhidrosis) |  |  |
| **Investigations** |  | Increase in blood alkaline phosphatase | Increased amylase |  | International normalised ratio increased (in patients treated with Vitamin K  antagonists) |

\*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

\*\* Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

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, 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, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Health Product Vigilance Center; HPVC

#### 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 <GENERIC NAME> in overdoses.

#### Only a small quantity of <GENERIC NAME> (<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.

1. **PHARMACOLOGICAL PROPERTIES**
   1. **Pharmacodynamic properties**

Pharmacotherapeutic group: Fluoroquinolones

ATC code: J01MA02 Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of <GENERIC NAME> 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 (Cmax) and the minimum inhibitory concentration (MIC) of <GENERIC NAME> 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* *Breakpoints (V 7.1, valid from 2017-03-10)*

|  |  |  |
| --- | --- | --- |
| **Microorganisms** | **Susceptible** | **Resistant** |
| Enterobacteria | S ≤ 0.25 mg/L | R > 0.5 mg/L |
| Pseudomonas spp.1 | S ≤ 0.5 mg/L | R > 0.5 mg/L |
| Acinetobacter spp.1 | S ≤ 1 mg/L | R > 1 mg/L |
| Staphylococcus spp.1 | S ≤ 1 mg/L | R > 1 mg/L |
| Haemophilus influenzae | S ≤ 0.06 mg/L | R > 0.06 mg/L |
| Moraxella catarrhalis | S ≤ 0.5 mg/L | R > 0.5 mg/L |
| Neisseria gonorrhoeae | S ≤ 0.03 mg/L | R > 0.06 mg/L |
| Neisseria meningitidis2 | S ≤ 0.03 mg/L | R > 0.06 mg/L |
| Non-species-related breakpoints | S ≤ 0.25 mg/L | R > 0.5 mg/L |

1 Breakpoints are based on high dose therapy (0.4 g x 3 i.v.)

2 Breakpoints apply only to use in the prophylaxis of meningococcal disease

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 <GENERIC NAME> susceptibility (for Streptococcus species see section 4.4)

|  |
| --- |
| **COMMONLY SUSCEPTIBLE SPECIES** |
| Aerobic Gram-positive micro-organisms  *Bacillus anthracis* (1) |
| 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* ($)  *Staphylococcus* spp. \*(2) |
| Aerobic Gram-negative micro-organisms  *Acinetobacter baumannii+*  *Burkholderia cepacia +\**  *Campylobacter* spp.*+\**  *Citrobacter freundii\**  *Enterobacter aerogenes,*  *Enterobacter cloacae \**  *Escherichia coli\**  *Klebsiella oxytoca,*  *Klebsiella pneumoniae\* Morganella morganii\**  *Neisseria gonorrhoeae\**  *Proteus mirabilis\* Proteus vulgaris\* Providencia* spp.  *Pseudomonas aeruginosa\**  *Pseudomonas fluorescens*  *Serratia marcescens\** |
| Anaerobic micro-organisms  Peptostreptococcus spp.  Propionibacterium acne |
| **INHERENTLY RESISTANT ORGANISMS** |
| Aerobic Gram-positive micro-organisms  Actinomyces  Enteroccus faecium  Listeria monocytogenes |
| Aerobic Gram-negative micro-organisms  Stenotrophomonas maltophilia |
| Anaerobic micro-organisms  Excepted as listed above |
| Other micro-organisms  Mycoplasma genitalium  Ureaplasma urealitycum |
| \* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications  + Resistance rate ≥ 50% in one or more EU countries  ($):Natural intermediate susceptibility in the absence of acquired mechanism of resistance  (1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on in-vitro susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the  following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax.  (2): Methicillin-resistant S. aureus 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 <GENERIC NAME> the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of <GENERIC NAME> 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 <GENERIC NAME> and its metabolites.

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

### A 60-minute intravenous infusion of 400 mg <GENERIC NAME> 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 Cmax similar to that observed with a 750 mg oral dose.

### 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.

*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.

|  |  |  |
| --- | --- | --- |
| **Excretion of ciprofloxacin (% of dose)** | | |
|  | **Intravenous Administration** | |
| **Urine** | **Faeces** |
| **Ciprofloxacin** | 61.5 | 15.2 |
| **Metabolites (M1-M4)** | 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 Cmax and AUC were not age-dependent (above one year of age). No notable increase in Cmax and AUC upon multiple dosing (10 mg/kg three times daily) was observed. In 10 children with severe sepsis Cmax 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, <GENERIC NAME> is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of <GENERIC NAME> *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, <GENERIC NAME> causes damage to the large weightbearing 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, <GENERIC NAME> caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

# PHARMACEUTICAL PARTICULARS

# List of excipients

# <REGARDING THE APPROVAL>

# Incompatibilities

Unless compatibility with other solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of ciprofloxacin solutions: 3.9 – 4.5).

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

* 1. **Shelf life**

<REGARDING THE APPROVAL>

* 1. **Special precautions for storage**

<REGARDING THE APPROVAL>

* 1. **Nature and contents of container**

<REGARDING THE APPROVAL>

* 1. **Special precautions for disposal and other handling**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION HOLDER**

<REGARDING THE APPROVAL>

1. **MARKETING AUTHORISATION NUMBER(S)**

<REGARDING THE APPROVAL>

1. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<REGARDING THE APPROVAL>

# DATE OF REVISION OF THE TEXT[[1]](#footnote-1)

# <REGARDING THE APPROVAL>

1. Ref: Ciprofloxacin, MHRA, 28/01/2021 [↑](#footnote-ref-1)