

Giroflox

PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

Giroflox

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for infusion contains 2 mg ciprofloxacin.

Excipients:

Each vial of 100 ml of solution for infusion contains 15.4 mmol (354 mg) sodium.

Each vial of 200 ml of solution for infusion contains 31 mmol (707.70 mg) sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear, colourless to slightly yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults :

- Broad spectrum antibiotic for infections caused by ciprofloxacin sensitive pathogens.

Children and adolescents:

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when there is no other alternative .

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents

4.2 Posology and method of administration

Posology

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 (see section 4.4)	Acute and complicated 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)
	Bacterial 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 including cases due to susceptible <i>Neisseria gonorrhoeae</i>	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</i>	400 mg twice daily	5 days

	dysenteriae type 1		
	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 caused by Gram-negative bacteria	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. 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

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 postexposure curative treatment for persons requiring parenteral treatment Drug administration should	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

begin as soon as possible after suspected or confirmed 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.

Patients 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 [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 (see section 6.6).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (listed in section 6.1).
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

The use of ciprofloxacin 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 ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see section 4.3).

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 the weight-bearing joints of immature animals. Safety data from a randomized 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 the 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 (**see section 4.8**).

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 (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

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. Ciprofloxacin 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.

Tendinitis and tendon rupture

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 but not limited to Achilles tendon), sometimes bilateral, may 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 (see section 4.8). 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 ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Patients with myasthenia gravis

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

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 a 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 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 Sjogren'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.

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 (see section 4.8).

Seizures

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 (see section 4.8).

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypoaesthesia, dysaesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin 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).

Psychiatric reactions

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. If depression, psychotic reactions, suicide-related thoughts or behaviour occur, ciprofloxacin should be discontinued.

Cardiac disorders

Since ciprofloxacin is associated with cases of QT prolongation (see section 4.8), caution should be exercised when treating patients at risk for torsade de pointes arrhythmia.

QT interval prolongation

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.

(See section 4.2 Elderly patients, section 4.5, section 4.8, section 4.9).

Dysglycaemia

As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in elderly 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, 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 (see section 4.8). 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 as described in section 4.2 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 (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 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 (see section 4.5). Co-administration of ciprofloxacin and tizanidine is contraindicated.

Methotrexate

The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5).

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 (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome), the sodium content of ciprofloxacin should be taken into account (see section 2).

4.5 Interaction with other medicinal products and other forms of 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) (see section 4.4).

Probenecid

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

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 (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 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 fludione).

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 (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 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).

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-desmethylozapine 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

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 (see section 4.4).

Zolpidem

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

Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or fetoneonatal 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.

Breast - feeding

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

4.7 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.

4.8 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.

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 (cannot be estimated from the available data)
Infections and infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and the lymphatic system		Eosinophilia	Leukopenia Anaemia, Neutropenia,	Haemolytic anaemia, Agranulocytosis,	

disorders			Leukocytosis, Thrombocytopenia, Thrombocytemia	Pancytopenia (life-threatening), Bone marrow depression (life- threatening)	
Immune system disorders			Allergic reaction, Allergic oedema / angioedema	Anaphylactic reaction,; Anaphylactic shock (life- threatening), (see section 4.4) Serum sickness- like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and nutrition disorders		Anorexia Decreased appetite	Hyperglycaemia Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section 4.4)
Psychiatric disorders (*)		Psychomotor hyperactivity / agitation	Confusion and disorientation, Anxiety reaction, Abnormal dreams, Depression, (potentially culminating in suicidal ideations/thoughts 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)	Mania, incl. hypomania
Nervous system disorders (*)		Headache, Dizziness, Sleep disorder, Taste disorder	Par- and Dysaesthesia, Hypoaesthesia, Tremor, Seizures (including status epilepticus see section 4.4) Vertigo,	Migraine, Disturbed coordination, Gait disturbance, Olfactory nerve disorder Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4)
Eye disorders			Visual disturbances	Visual colour	

(*)			(e.g. diplopia)	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 section 4.4 and 4.9).
Vascular disorders (**)			Vasodilation, Hypotension, Syncope	Vasculitis	
Respiratory, thoracic and mediastinal disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal disorders	Nausea, Diarrhoea	Vomiting, Gastrointestinal and abdominal pain, Dyspepsia, Flatulence,	Antibiotic-associated colitis (very rarely with possible fatal outcome) (see section 4.4)	Pancreatitis	
Hepato-biliary disorders		Increase in transaminases, 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 life-threatening), Toxic epidermal necrolysis (potentially life-threatening)	Acute Generalised Exanthematous Pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders (*)		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain),	Myalgia Arthritis, Increased muscle tone and cramping	Muscular weakness, Tendinitis Tendon ruptures	

		Arthralgia		(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 administration site conditions(*)	Injection and infusion site reactions (only intravenous administration)	Asthenia, Fever	Oedema, Sweating (hyperhidrosis)		
Investigations		Increased blood alkaline phosphatase	Prothrombin level abnormal, 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 (arthralgia, arthritis) 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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form <https://sideeffects.health.gov.il/>

4.9 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 of overdose may include dizziness, tremor, headaches, 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 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
Enterobacteriaceae	$S \leq 0.25 \text{ mg/L}$	$R > 0.5 \text{ mg/L}$
Salmonella spp	$S \leq 0.06 \text{ mg/L}$	$R > 0.06 \text{ mg/L}$
Pseudomonas spp.	$S \leq 0.5 \text{ mg/L}$	$R > 0.5 \text{ mg/L}$
Acinetobacter spp.	$S \leq 1 \text{ mg/L}$	$R > 1 \text{ mg/L}$
Staphylococcus spp. ¹	$S \leq 1 \text{ mg/L}$	$R > 1 \text{ mg/L}$
Haemophilus influenza	$S \leq 0.06 \text{ mg/L}$	$R > 0.06 \text{ mg/L}$
Moraxella catarrhalis	$S \leq 0.125 \text{ mg/L}$	$R > 0.125 \text{ mg/L}$
Neisseria gonorrhoeae	$S \leq 0.03 \text{ mg/L}$	$R > 0.06 \text{ mg/L}$
Neisseria meningitidis	$S \leq 0.03 \text{ mg/L}$	$R > 0.03 \text{ mg/L}$
Non-species related breakpoints*	$S \leq 0.25 \text{ mg/L}$	$R > 0.5 \text{ mg/L}$

1 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.

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

COMMONLY SUSCEPTIBLE SPECIES
<u>Aerobic Gram-positive micro-organisms</u>
Bacillus anthracis (1)
<u>Aerobic Gram-negative micro-organisms</u>
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
<u>Anaerobic micro-organisms</u>
Mobiluncus
<u>Other micro-organisms</u>
Chlamydia trachomatis (\$)
Chlamydia pneumoniae (\$)
Mycoplasma hominis (\$)
Mycoplasma pneumoniae (\$)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM

<u>Aerobic Gram-positive micro-organisms</u> Enterococcus faecalis (\$) Staphylococcus spp. (2)
<u>Aerobic Gram-negative micro-organisms</u> 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*
<u>Anaerobic micro-organisms</u> Peptostreptococcus spp. Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
<u>Aerobic Gram-positive micro-organisms</u> Actinomyces Enterococcus faecium Listeria monocytogenes
<u>Aerobic Gram-negative micro-organisms</u> Stenotrophomonas maltophilia
<u>Anaerobic micro-organisms</u> Excepted as listed above
<u>Other micro-organisms</u> Mycoplasma genitalium Ureaplasma urealyticum
* 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 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.

5.2 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 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 (M ₁ -M ₄)	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%.

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Lactic acid Sol. 90%
Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities

- This medicinal product is incompatible with injection solutions (e.g. penicillins, heparin solutions) which are chemically or physically unstable at pH of 3.9 - 4.5.
- The solution should be clear. Do not use if particles are present.
- Unless compatibility is proven, the infusion should always be administered separately.
- Solutions containing ciprofloxacin should not be mixed with or added to solutions containing other agents unless compatibility has been proven.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials
From a microbiological point of view, the product should be used immediately on opening.

6.4 Special precautions for storage

- Store below 30°C . Do not refrigerate or freeze
- Keep the vial in the original container until time of use in order to protect from light.
- The infusion solution must be used immediately after opening.

For ease of use the infusion vial stopper should be penetrated in the central ring.
Penetration of the outer ring may result in damage to the vial stopper.
Any unused solution should be disposed off.

6.5 Nature and contents of container

Giroflox 2 mg/ml solution for infusion is packaged in a colorless, transparent plastic bottle with inner cap, rubber stopper and flip cap.

Pack sizes:

1 or 10 x 100 ml

1 or 10 x 200 ml

It's possible that not all the presentations are commercialized.

6.6 Special precautions for disposal and other handling

Intravenous infusion:

The use of freshly prepared solutions is recommended (see section 6.3).

- The solution should be visually inspected for particulate matter and discoloration prior to administration. Only clear and colourless or slightly yellow solution should be used.
- For single use only.
- Unless compatibility is proven, the infusion solution should always be administered separately.
- Any unused solution and the vials should be adequately disposed of, in accordance with local requirements.

7 MANUFACTURER

Cooper Pharmaceuticals, 64 Aristovoulou Str. 11853 Athens, Greece

For:

Tecnimede – Sociedade Tecnico Medicinal, S.A., Portugal

8 REGISTRATION HOLDER

BioAvenir Ltd.,

1 David Hamelech St., Herzelia Pituach.

9 REGISTRATION NUMBER

133-31-30984

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