Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT (FPP)

CIPRONAT® IV

Ciprofloxacin

1.1. Strength 200 mg/100 ml

1.2. Pharmaceutical form Solution for infusion (IV)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle with 100 ml solution contains 200 mg ciprofloxacin.

Excipients with known effect: sodium chloride
The content of sodium chloride is 900 mg (15.4 mmol)

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

Cipronat 200 mg/100 ml 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 ciprofloxacin before initiating therapy. Consideration should be given to official guidance on the appropriate use if antibacterial agents.

Indications for adults

- Lower respiratory tract infections due to Gram-negative bacteria
    - exacerbation of chronic obstructive pulmonary disease
    - 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
- Urinary infections
    - acute pyelonephritis
    - complicated pyelonephritis
    - bacterial prostatitis
- Epididymo-orchitis including cases due to susceptible *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including infections due to *Neisseria gonorrhoeae*
  When the above-mentioned infections of the genital tract are suspected or confirmed with *Neisseria gonorrhoeae*, it is particularly important to have information on the prevalence of local resistance of this bacterium to ciprofloxacin and to confirm its susceptibility to the antibiotic through microbiological tests.
- 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
- External malignant otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Anti-infectious prophylaxis in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Indications for children and adolescents

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

Ciprofloxacin 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 doctors who are experienced in the treatment of cystic fibrosis and/or sever infections in children and adolescents (see sections 4.4 and 5.1)

4.2. Posology and mode of administration

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

After intravenous initiation of the treatment, the treatment can be switched to oral treatment with tablets of suspension if clinically indicated and according to the doctor's advice. IV treatment should be followed by oral route as soon as possible. In severe cases or if the patient is unable to swallow tablets (e.g. patients on enteral nutrition), it is recommended to start therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

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

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

For Adults

Indication		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infection of the lower respiratory tract		400 mg Two or three times daily	7 to 14 days
Infections of the upper respiratory tracts	Acute exacerbations of chronic sinusitis	400 mg Two or three times daily	7 to 14 days
	Chronic suppurative otitis	400 mg Two or three times daily	7 to 14 days
	External malignant otitis	400 mg Three times daily	28 days up to 3 months
Urinary infections	Acute and complicated pyelonephritis	400 mg Two or three times daily	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Bacterial prostatitis	400 mg Two or three times daily	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg Two or three times daily	at least 14 days
Infections of the gastro-	Diarrhoea caused by bacterial	400 mg , two times daily	1 day

Indication		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
intestinal tract and intra-abdominal infections	pathogens including *Shigella spp.* Other than *Shigella dysenteriae* type 1 and empirical treatment of severe traveller's disease		
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg , two times daily	5 days
	Diarrhoea caused by *Vibrio choleraa*	400 mg , two times daily	3 days
	Typhoid fever	400 mg two times daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg , two to three times daily	5 to 14 days
Infections of the skin and soft tissue		400 mg , two to three times daily	7 to 14 days
Infections of the bones and joints		400 mg , two to three times daily	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 , two to three times daily	Therapy should be continued aver the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment.		400 mg two time daily	60 days from the confirmation of *Bacillus anthracis* exposure

4.2.2. Special populations

Elderly patients

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

Patients with renal impairment

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

Creatine Clearance [ml/min/1,73 m^2]	**Serum creatine [µmol/l]**	**Intravenous dose [mg]**
> 60	< 124	See usual dose
30-60	124 à 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h
Patients on hemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

Patients with hepatic impairment

A dose adjustment in patients with impaired hepatic function is not required.

4.2.3. Pediatric population

Indication	**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Cystic fibrosis	10 mg/kg bodyweight Three times daily with a maximum of 400 mg per dose	10 to 14 days
Complicated urinary tract infection and acute pyelonephritis	6 mg/kg bodyweight to 10 mg/kg bodyweight Three time daily with a maximum of 400 mg per dose	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment. DDrug administration should begin as soon as possible after suspected or confirmed exposure	10 mg/kg body weight to 15 mg/kg bodyweight Two time daily with a maximum of 400 mg per dose	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infctions	10 mg/kg bodyweight Three time daily with a maximum of 400 mg per dose	

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

4.2.4. Method of administration

Cipronat 200mg/100ml solution for IV should be checked visually prior to use. It must not be used if the solution is cloudy.

Cipronat IV solution for infusion should be administered by intravenous infusion.
For children the duration of the infusion is 60 minutes.
In adult patients infusion time is 30 minutes for Cipronat 200 mg/100 ml solution.
Slow infusion into a large vein will minimise patients discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion fluids (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 warning and precautions for use

4.4.1. General information

The use of ciprofloxacin should be avoided in patients who have experience serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with ciprofloxacin should be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

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. Ciprofloxacin should be administered 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 world. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones. The single dose of ciprofloxacin that can be used in uncomplicated cystitis in non-menopausal women should be associated with lower efficacy than long-term treatment. This must be taken into account, especially considering the increased rate of resistance of *Escherichia coli* to quinolones.

Intra-abdominal infections

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

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.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactic 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 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 (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 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, Behets 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.

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, hypaesthesia, dysesthesia, 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. In the occurrence of such cases, ciprofloxacin should be discontinued.

Cardiac disorders

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

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

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations. (See section 4.2 Elderly patients, section 4.5, section 4.8, section 4.9).

Dysglycemia

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. 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.

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, aglomelatine). 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 contra-indicated.

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
Cipronat 200 mg/100 ml solution for infusion (IV) contains 354.2 mg sodium per bottle (or 3.54 mg of sodium per ml).
The composition of Cipronat IV is considered to be rich in sodium.
In patients for whom a control of sodium intake is medically necessary (in case of congestive heart failure, renal failure, nephrotic syndrome, etc.) and for patients on a low salt diet, the sodium content of this solution should be taken into account.

4.4.2. Pediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by medical doctors 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 (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.

4.5. Interactions with other medicinal products and other forms of interactions

Effects of other medicinal 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.

Cyclosporine
A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporine 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.

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 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-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (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 'Cytochrome P450' in section 4.4).

Zolpidem

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

4.6. Fertility, pregnancy and lactation

4.6.1. Fertility

See section 5.3

4.6.2. Pregnancy

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

4.6.3. Lactation

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 the 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

Summary of the safety profile

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.

Tabulated summary of adverse reaction

System organ class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1000 to < 1/100	**Rare** ≥ 1/10000 à < 1/1000	**Very rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and infestations		Mycotic surinfections			
Blood and Lymphatic system disorders		Eosinophilia	Leukopenia Anemia Neutropenia Leukocytosis Thrombo-cytopenia Thrombo-cytemia	Hemolytic anemia Agranulocytosis 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		Decreased appetite	Hyperglyemia Hypoglycemia (see section 4.4)		Hypoglycemic coma (se section 4.4)
Psychiatric disorders*		Psychomotor hyperactivity /agitation	Confusion and disorientation Anxiety reaction	Psychotic reaction (potentially culminating in suicidal	Mania including hypomania

System organ class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1000 to < 1/100	**Rare** ≥ 1/10000 à < 1/1000	**Very rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
			Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide (see section 4.4) Hallucinations	ideations/thoughts or suicide attempts and completed suicide (see section 4.4)	
Nervous system disorders*		Headache Dizziness Sleep disorders Taste disorders	Paresthesia and dysesthesia Hypoesthesia Tremor Seizures (incl. status epilepticus, see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuro-pathy (see section4.4)
Eye disorders*			Visual disturbances (e.g. diplopia)	Visual colour distortions	
Ear and Labyrinth disorders*			Tinnitus Hearing loss/Impaired hearing		
Cardia disorders**			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients

System organ class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1000 to < 1/100	**Rare** ≥ 1/10000 à < 1/1000	**Very rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
					with risk factors for QT prolongation) ECG QT prolongation (see sections 4.4 and 4.9)
Vascular disorders**			Vasodilation Hypotension Syncope	Vasculitis	
Respiratory Thoracic and Mediastinal disorders			Dyspnea (incl. asthmatic condition)		
Gastrointestinal disorders	Nausea Diarrhea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence	Antibiotic associated colitis (very rarely with fatal outcome) (see section 4.4)	Pancreatitis	
Hepatobiliary disorders		Increase in trans-aminases 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 Pruritis Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening)	Acute generalized exanthema-tous pustulosis (ARGP); Drug raction with eosinophilia and systemic symptoms (DRESS)

System organ class	**Common** ≥ 1/100 to < 1/10	**Uncommon** ≥ 1/1000 to < 1/100	**Rare** ≥ 1/10000 à < 1/1000	**Very rare** < 1/10 000	**Frequency not known** (cannot be estimated from available data)
				Toxic epidermal necrolysis (potentially life-threatening)	
Musculoskeletal and Connective tissue disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon (see section 4.4) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary disorders		Renal impairment	Renal failure Hematuria Crystalluria (see section 4.4) Tubulointer-stitial nephritis		
General disorders and Administration site conditions*	Injection and infusion site reactions (only IV ad-ministration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalized ratio increased (in patients treated with vit 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, Thrombocythemia, Confusion and disorientation, Hallucinations, Par- and dysesthesia, 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

Pediatric 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).

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 in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria.

Reversible renal toxicity has been reported.

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

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.
In the event of overdose, symptomatic treatment sho ld be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group and ATC code**:** Fluoroquinolones ATC **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**
Enterobacteria's	S ≤ 0,25 mg/l	R > 0,5 mg/l
Salmonella spp	S ≤ 0,06 mg/l	R > 0,06 mg/l
Pseudomonas spp.	S ≤ 0.5 mg/l	R > 0,5 mg/l
Acinetobacter spp.	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 ≤ 0,125 mg/l	R > 0,125 mg/l
Neisseria gonorrhoeae	S ≤ 0,03 mg/l	R > 0,06 mg/l
Neisseria meningitidis	S ≤ 0,03 mg/l	R > 0,03 mg/l
Non-species-related breakpoints [2]	S ≤ 0,25 mg/l	R >0,5 mg/l

[1] *Staphylococcus* spp. - breakpoints for ciprofloxacin relate to high dose therapy.

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

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

Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species 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-organism
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 acnes

INHERENT 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.

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 non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity

but to a lower degree than the parent compound.
Ciprofloxacine is known to be a moderate inhibitor of CYO 450 1A2 iso-enzymes.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and to a smaller extent via faeces.

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.

Pediatric population

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

- Lactic acid (90%)
- Sodium chloride
- Hydrochloric acid 1N
- Water for injections

6.2. Incompatibilities

This medicine should not be mixed with other medicinal products except for those mentioned in section 6.6.
Unless compatibility with other solutions/medicinal products has been confirmed, the infusion solution should always be administered separately. Visual sings of incompatibility are e.g. precipitation, clouding and discoloration.
Incompatibility occurs with all infusion solutions/medicinal products that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions) especially in combination with solutions to an alkaline pH (pH of ciprofloxacin infusion solutions is 3.9 to 4.5)

6.3. Shelf life

3 years

From a microbiological point of view, even if the method of opening and mixing with other drugs prevents any risk of contamination, the product should be used immediately. If it is not used immediately, the in-use conditions and time of storage are the responsibility of the user.

6.4. Special precautions for storage

Store below 30°C protected from light.
Do not refrigerate or freeze.

6.5. Nature and contents of container

Colourless glass vial with 100 ml of sterile aqueous solution for IV infusion corresponding to 200 mg of ciprofloxacin. The vial is closed with a bromobutyl rubber stopper, sealed with an aluminium cap.

Box containing 1 vial.

6.6. Special precautions for disposal and other handlings

The solution for infusion of ciprofloxacin is compatible with Ringer's solution, Ringer lactate solution, glucose solutions 5% and 10%, fructose solutions 5% and 10%.

When a ciprofloxacin infusion solution is mixed with a compatible infusion solution, the solution should be administered promptly after mixing for reasons of microbial contamination and sensitivity to light.

Since the infusion solution is sensitive to light, the vials will need to be taken out of their box just before use. In daylight, the full effectiveness of the solution is guaranteed for a period of 3 days.

Vial for single use.

No special requirements for disposal.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

7.1. Marketing Authorisation Holder

Dafra Pharma GmbH, Mühlenberg 7, 4052 Basel, Switzerland.

7.2. Manufacturer

Pharmathen S.A. 153 51 Pallini-Attiki, Greece
Site: DEMO S.A., 21st km National Road Athens-Lamia, 145 68 Kryoneri, Athens, Greece

8. MARKETING AUHORISATION NUMBER

See list of MAs per country

9. DATE OF FIRST REGISTRATION

See list of MAs per country

10. DATE OF REVISION OF TEXT

05/2021