1.4 Product Information

1.4.1 Prescribing information (Summary of Product Characteristics)

1. Name of the medicinal product

Ciprofloxacin Tablets USP 500 mg

2. Qualitative and quantitative composition

Each tablet contains ciprofloxacin 500mg as the hydrochloride.

For excipients see 6. 1.

3. Pharmaceutical form

Tablets.

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin tablets 500 mg are 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 commencing therapy.

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

Adults

• Lower respiratory tract infections due to Gram-negative bacteria

- exacerbations of chronic obstructive pulmonary disease

- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis

- pneumonia

In exacerbations of chronic obstructive pulmonary disease Ciprofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.

• Chronic suppurative otitis media

• Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria

• Uncomplicated acute cystitis

In uncomplicated acute cystitis Ciprofloxacin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment

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of these infections.

• Acute pyelonephritis

• Complicated urinary tract infections

• Genital tract infections

• Gonococcal uretritis and cervicitis due to susceptible Neisseria gonarrhoeae

• Epididymo-orchitis including cases due to susceptible Neisseria gonorrhoeae

• Pelvic inflammatory disease including cases due to susceptible Neisseria gonorrhoeae

• In the above genital tract infections when thought or known to be due to Neisseria gonorrhoeae it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

• Infections of the gastro-intestinal tract (e.g. travellers' diarrhoea)

• Intra-abdominal infections

• Infections of the skin and soft tissue caused by Gram-negative bacteria

• Malignant external otitis

• Infections of the bones and joints

• Treatment of infections in neutropenic patients

• Prophylaxis of infections in neutropenic patients

• Prophylaxis of invasive infections due to Neisseria meningitides

• Inhalation anthrax (post-exposure prophylaxis and curative treatment)

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

Paediatric population

• Broncho-pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis

• Complicated urinary tract infections and acute pyelonephritis

• Inhalation anthrax (post-exposure prophylaxis and curative treatment)

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 physicians who are experienced in the treatment of cystic

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fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

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.

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

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

Adults

Indications		Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Infections of the lower respiratory tract		500mg twice daily to 750 mg twice daily	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg twice daily to 750 mg twice daily	7 to 14 days
	Chronic suppurative otitis media	500 mg twice daily to 750 mg	7 to 14 days

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		twice daily	
	Malignant external otitis	750 mg twice daily	28 days up to 3 months
Urinary tract infections	Uncomplicated cystitis	250mg twice daily to 500 mg twice daily	3 days
		In pre-menopausal women, 500 mg single dose may be used	
	Complicated cystitis, Uncomplicated pyelonephritis	500 mg twice daily	7 days
	Complicated pyelonephritis	500 mg twice daily to 750 mg twice daily	at least 10 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	500 mg twice daily to 750 mg twice daily	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Genital tract infections	Gonococcal uretritis and cervicitis	500 mg as a single dose	1 day (single dose)
	Epididymo-orchitis and pelvic inflammatory diseases	500 mg twice daily to 750 mg twice daily	at least 14 days
Infections of the gastro-intestinal tract and intraabdominal infections	Diarrhoea caused by bacterial pathogens including Shigella spp. other than Shigella dysenteriae type 1 and empirical treatment of severe travellers' diarrhoea	500 mg twice daily	1 day

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	Diarrhoea caused byShigella dysenteriae type 1	500 mg twice daily	5 days
	Diarrhoea caused byVibrio cholerae	500 mg twice daily	3 days
	Typhoid fever	500 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	500 mg twice daily to 750 mg twice daily	5 to 14 days
Infections of the skin and soft tissue		500mg twice daily to 750 mg twice daily	7 to 14 days
Bone and joint infections		500 twice daily to750 mg twice daily	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		500 mg twice daily to 750 mg twice daily	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to Neisseria meningitidis		500 mg as a single dose	1 day (single dose)
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure		500 mg twice daily	60 days from the confirmation of Bacillus anthracisexposure

Paediatric population

Indications	Daily dose in mg	Total duration of treatment (potentially including initial

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		parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily with a maximum of 750 mg per dose	10 to 14 days
Complicated urinary tract infections and pyelonephritis	10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose	10 to 21 days
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons able to receive treatment by oral route when clinically appropriate. Drug administration should begin as soon as possible after suspected or confirmed exposure	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose	60 days from the confirmation of Bacillus anthracis exposure
Other severe infections	20 mg/kg body weight twice daily with a maximum of 750 mg per dose	According to the type of infections

Elderly Patients

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

Renal and hepatic impairment

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

Creatinine clearance [mL/min/1.73 m²]	Serum creatinine [μmol/L]	Oral Dose [mg]
> 60	< 124	See Usual Dosage
30-60	124 to 168	250-500 mg every 12 h

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< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

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

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

Method of administration:

The tablets are to be swallowed unchewed with fluid. They can be taken independent of meal times. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice) (see section 4.5).

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.

4.3 Contraindications

• Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

• Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

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 in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately

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consult a physician in an emergency department.

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 also 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

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae isolates.

Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should 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.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of Escherichia

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coli to quinolones.

Intra-abdominal infections

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

Travellers' diarrhoea

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

Infections of the bones and joints

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

Inhalational anthrax

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

Paediatric population

The use of ciprofloxacin in children and adolescents should follow available official guidance.

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

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue (see section 4.8).

Broncho-pulmonary infections in cystic fibrosis

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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 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.

Musculoskeletal System

Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment,

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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 (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

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

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).

Central Nervous System

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thought culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.

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

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

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irreversible condition (see section 4.8).

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, 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 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

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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). Co-administration of ciprofloxacin and tizanidine is contra-indicated. 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).

Methotrexate

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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.

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 [INN] 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)

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. [INN] 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.

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).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin.

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Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products

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

Probenecid

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

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of ciprofloxacin

Effects of ciprofloxacin on other medicinal products:

Tizanidine

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

Methotrexate

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

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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.

Ciclosporin

A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin 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. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin k antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

Duloxetine

In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors

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of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration (see section 4.4).

Ropinirole

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

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised (see section 4.4).

Sevelamer

The bioavailability of ciprofloxacin is reduced by the concomitant administration with sevelamer (up to 50%), therefore, it is recommended that the two should not be taken concomitantly.

Sildenafil

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

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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

Pregnancy

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

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

a) Summary of the safety profile

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

b) Tabulated list of adverse reactions

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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 available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Immune System Disorders			Allergic reaction Allergic oedema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening)	

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				(see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia (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 Hypomania
Nervous System Disorders*		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus (see section 4.4)	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial	Peripheral neuropathy and polyneuropathy (see section 4.4)

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			Vertigo	hypertension and pseudotumour cerebri	
Eye Disorders *			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders*			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and 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			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal	Antibiotic associated diarrhoea including	Pancreatitis	

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		pains Dyspepsia Flatulence	pseudomembranous colitis (see section 4.4)		
Hepatobiliary 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, Connective Tissue and Bone Disorders*		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of	

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				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*		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in 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).

Paediatric population

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

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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, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

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

Therapeutic classification: J 01 MA 02

Activity:

Ciprofloxacin is a synthetic 4-quinolone derivative antibacterial agent of the fluoroquinolone class.

Mechanism of action:

As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Spectrum of activity:

Breakpoints:

BSAC: S[1ml/L; Rμ 2mg/l, except Pseudomonas R μ 8mg/ml and UTI R μ 8mg/L.

NCCLS: S [1mg/1; I = 2mg/l; R μ 4mg/l.

Susceptibility

The prevalence of the acquired resistances can vary for some species geographically and with

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time. Therefore, it is important to obtain information on local resistance patterns, particularly when treating more severe infections.

The information provided below gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

Organism	Prevalence of Resistance
Sensitive:	
Gram-positive bacteria	
Staphylococcus aureus (methicillin sensitive)	0-14%
Streptococcus agalactiae	0-17%
Gram-negative bacteria	
Acinetobacter baumanii	6-93%
Acinetobacter spp.	14-70%
Aeromonas hydrophila	
Campylobacter jejuni/coli	0-82%
Citrobacter freundii	0-4%
Enterobacter aerogenes	
Enterobacter cloacae	0-3%
Enterobacter spp	3-13%
Escherichia coli	2-7%
Haemophilus influenzae	0-1%
Klebsiella spp.	2-21%
Moraxella catarrhalis	
Morganella morganii	1-2%
Neisseria gonorrhoeae	5%
Plesiomonas shigelloides	
Proteus mirabilis	0-10%
Proteus vulgaris	4%

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Providencia spp.	4%
Pseudomonas aeruginosa	1-28%
Salmonella spp.	
Salmonella typhi	0-2%
Serratia liquefaciens	
Serratia marcescens	23%
Shigella spp	
Vibrio spp	
Yersinia enterocolitica	
Anaerobes*	
Peptococcus spp.	-
Peptostreptococcus spp.	-
Veillonella parvula	-
Other pathogens	
Legionella pneumophila	-
Intermediate	
Viridans streptoeocci	5-9%
Streptococcus pneumonziae	2.8%
Streptococcus pyogenes	2.8%
Other pathogens	
Chlamydia spp	-
Resistant	
Gram-positive aerobes	
Enterococcus spp	-
Staphylococcus aureus (methicillin resistant)	48-90%
Gram-negative aerobes	

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Stenotrophomonas maltophila	-
Flavobacterium menmgosepticum	-
Nocardia asteroides	-
Anaerobes	
Bacteroides_fragilis	-
Bacteroides thetaiotaomicron	-
Clostridium difficile	-

* Ciprofloxacin is not considered the drug of first choice for treatment of infections with anaerobes.

In-vitro investigations have shown that resistance to ciprofloxacin is commonly due to mutations in bacterial topoisomerases and usually develops slowly and gradually ("multiple-step" type).

Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the class. Impermeability and/or drug efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various drugs within the class and the affinity of transport systems for each drug.

5.2 Pharmacokinetic properties

Absorption

After oral administration, ciprofloxacin is predominantly absorbed from the duodenum and upper jejunum, and reaches peak serum concentrations within 60-90 min. After single doses of 250mg and 500mg Cmax values are about 0.8-2.0mg/1 and 1.5-2.9mg/1 respectively

The absolute bioavailability is approximately 70 to 80%. Cmax- and AUC-values are proportionally increased with the dose.

Food intake has no effect on the plasma concentration profile of ciprofloxacin.

Distribution

The steady-state volume of distribution of ciprofloxacin is 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma in

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non-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravasal space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.

Metabolism / Elimination

Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5ml/min/kg, and total clearance amounts to 8-10ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.

Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 show antibacterial activity comparable with or smaller than nalidixic acid. M 4 with the lowest quantity, has an antimicrobial activity very much corresponding to norfloxacin.

Excretion after oral administration (in % of the ciproftoxacin dose):

	urine	faeces
Ciprofloxacin	44.7	25.0
Metabolites	11.3	7.5

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

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

5.3 Preclinical safety data

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals. Other preclinical effects were observed only at exposures, sufficiently in excess of the maximum human exposure, that make concern for human safety negligible in respect of animal data.

6. Pharmaceutical particulars

6.1 List of excipients

Corn starch

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Sucrose

Microcrystalline Cellulose (MCC)

Sodium Starch Glycolate (CMC-Na)

Calcium Hydrophosphate

Magnesium stearate (MS)

Hypromellose (HPMC)

Polyethylene glycol 6000

Talc

Titanium dioxide

Ethanol**

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Do not store above 30 °C. Store in the original packaging.

6.5 Nature and contents of container

PVC and Al foil blister, 10 tablet/blister 100 blister/box,

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorisation holder

Reyoung Pharmaceutical Co., Ltd

No.1 Ruiyang Road, Yiyuan County, Shandong Province

8. Marketing authorisation number(s)

Lu 20160062

9. Date of first authorisation/renewal of the authorisation

24/06/2015

10. Date of revision of the text

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