Summary of Product Characteristics

1. Name of the medicinal product

Cipro-Denk 500 mg film-coated tablets

2. Qualitative and quantitative composition

1 film-coated tablet contains 500 mg ciprofloxacin (as ciprofloxacin hydrochloride).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets for oral use

White, oblong film-coated tablets with a score on both sides and imprint “Cipro 500” on one side.

The tablet can be divided into equal doses.

4. Clinical particulars

4.1 Therapeutic indications

Cipro-Denk 500 is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Before the start of treatment, particular consideration should be given to the available information on resistance.

The official guidelines governing proper use of antimicrobial active ingredients are to be considered when using ciprofloxacin.

Adults

- Lower respiratory tract infections caused by Gram-negative bacteria:
  - exacerbations of chronic obstructive lung disease (COPD)
  - bronchopulmonary infections in cystic fibrosis or in bronchiectasis
  - pneumonia
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially when caused by Gram-negative bacteria
- Infections of the urinary tract including Gonococcal urethritis caused by suspectible *Neisseria gonorrhoeae*

- Genital trackt infections
  - gonococcal cervicitis caused by suspectible *Neisseria gonorrhoeae*
  - epididymo-orchitis, including cases caused by suspectible *Neisseria gonorrhoeae*
  - pelvic inflammatory disease, including infections caused by suspectible *Neisseria gonorrhoeae*

- Infections of the gastrointestinal tract (e.g. travellers' diarrhoea)

- Intra-abdominal infections

- Infections of the skin and soft tissues, caused by Gram-negative bacteria

- Malignant external otitis

- Infections of the bones and joints

- Prophylaxis of invasive infections caused by *Neisseria meningitidis*

- After inhalation of the pathogen Bacillus anthracis (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.

Children and adolescents

- Bronchopulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*

- Complicated urinary tract infections and pyelonephritis

- Immediate therapy and treatment of anthrax following inhalation of the pathogen *Bacillus anthracis* (post-exposure prophylaxis and curative treatment)

Ciprofloxacin can also be used for the treatment of severe infections in children and adolescents, whenever this is deemed necessary.

Treatment should be initiated only by a physician experienced in the treatment of cystic 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 of Cipro-Denk 500 is determined according to the type and severity of the infection, the susceptibility of the causative organism(s) as well as age, renal function of the patient and body weight of children and adolescents. Treatment may be initiated by oral or parenteral administration depending on the patient's condition.

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

The treatment of infections caused by certain pathogens (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci*) may require higher ciprofloxacin doses and co-administration of other appropriate antibacterial agents.

The treatment of certain infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of the bones and joints) may, depending on the pathogen, require adjuvant administration of other appropriate antimicrobial agents.

The following dosage recommendations serve as guidelines and apply only to oral administration of ciprofloxacin. Other dosage recommendations apply to parenteral use of ciprofloxacin.

Adults
The dosage for adults ranges from 100 and 750 mg of ciprofloxacin two times a day.

Therapeutic indications		**Daily dose of ciprofloxacin in mg**	**Total duration of treatment (including any initial parenteral treatment with ciprofloxacin)**
Infections of the lower respiratory tract		500 mg two times a day up to 750 mg two times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	500 mg two times a day up to 750 mg two times a day	7 to 14 days
	Chronic suppurative otitis media	500 mg two times a day up to 750 mg two times a day	7 to 14 days
	Malignant external otitis	750 mg two times a day	28 days up to 3 months
Infections of the urinary tract (see section 4.4)	Uncomplicated cystitis	250 mg two times a day up to 500 mg two times a day	3 days
		In pre-menopausal women, 500 mg single dose may be used.	
	Complicated cystitis, uncomplicated pyelonephritis	500 mg two times a day	7 days
	Complicated pyelonephritis	500 mg two times a day up to 750 mg two times a day	at least 10 days, under certain circumstances (such as abscesses), a treatment period beyond 21 days is possible
	Gonococcal urethritis	500 mg as single dose	1 day (single dose)
Infections of the genital tract	Gonococcal cervicitis	500 mg as single dose	1 day (single dose)
	Prostatitis	500 mg two times a day up to 750 mg two times a day	4 weeks (acute) up to 4 to 6 weeks (chronic)

Therapeutic indications		**Daily dose of ciprofloxacin in mg**	**Total duration of treatment (including any initial parenteral treatment with ciprofloxacin)**
	Epididymo-orchitis and pelvic inflammatory disease	500 mg two times a day up to 750 mg two times a day	at least 14 days
Infections of the gastrointestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp., excluding *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	500 mg two times a day	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	500 mg two times a day	5 days
	Diarrhoea caused by *Vibrio cholerae*	500 mg two times a day	3 days
	Typhoid fever	500 mg two times a day	7 days
	Intra-abdominal infections caused by Gram-negative bacteria	500 mg two times a day up to 750 mg two times a day	5 to 14 days
Infections of the skin and soft tissues		500 mg two times a day up to 750 mg two times a day	7 to 14 days
Infections of the bones and joints		500 mg two times a day up to 750 mg two times a day	No more than 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection Ciprofloxacin should be combined with appropriate antibacterial agents in accordance with official guidelines		500 mg two times a day up to 750 mg two times a day	The therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections caused by *Neisseria meningitidis*		500 mg as single dose	1 day (single dose)
Inhalation of anthrax pathogens –		500 mg two times a day	60 days from confirmation of

Therapeutic indications	Daily dose of ciprofloxacin in mg	Total duration of treatment (including any initial parenteral treatment with ciprofloxacin)
post-exposure prophylaxis and curative treatment for persons capable of receiving oral treatment, if clinically required. The treatment should be started as quickly as possible after suspected or confirmed exposure.		*Bacillus anthracis* exposure

Children and adolescents

Therapeutic indications	Daily dose of ciprofloxacin in mg	Total duration of treatment (including any initial parenteral treatment with ciprofloxacin)
Cystic fibrosis	20 mg/kg body weight twice daily, with a maximum single dose of 750 mg	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 single dose of 750 mg	10 to 21 days
Inhalation of anthrax pathogens – post-exposure prophylaxis and curative treatment for persons capable of receiving oral treatment, if clinically required. The treatment should be started as quickly 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 single dose of 500 mg	60 days from confirmation of *Bacillus anthracis* exposure
Other severe infections	20 mg/kg body weight twice daily, with a maximum single dose of 750 mg	Depending on the type of infection

Elderly patients

The dosage for elderly patients should be determined by the severity of the illness and the creatinine clearance.

Patients with impaired hepatic and/or renal function

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

creatinine clearance [ml/min/1,73m²]	serum creatinine [µmol/l]	oral dose [mg]
> 60	< 124	See usual dosage.
30–60	124 to 168	250-500 mg every 12 hours
< 30	> 169	250-500 mg every 24 hours
Patients on haemodialysis	> 169	250-500 mg every 24 hours (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 hours

A dosage adjustment is not required for slightly to moderately impaired hepatic function.

There are no studies available on dosage in children with impaired renal and/or hepatic function.

Method of administration
The film-coated tablets have to be swallowed whole with sufficient fluids. They can be taken with or without a meal. Taking the medication in a fasting condition accelerates the absorption of the active ingredient.
Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or with mineral-enriched beverages (e.g. calcium-enriched orange juice) (see section 4.5).

In severe cases, or if the patient is incapable of taking tablets (e.g. in patients on enteral nutrition), it is recommended that therapy be commenced with intravenously administered ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to the active substance or other antibiotics of the quinolone type or to any of the excipients listed in section 6.1.
- concomitant administration of tizanidine (see section 4.5)
- in patients who have already suffered from tendon complaints in association with the administration of antibiotics from the same class of compounds

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suitable for the treatment of severe infections and infections that might be caused by Gram-positive or anaerobic pathogens. In such cases, ciprofloxacin must be combined with other appropriate antibacterial agents.

Streptococcal infections (including Streptococcus pneumoniae)
Due to its insufficient efficacy, ciprofloxacin is not recommended for the treatment of streptococcal infections.

Infections of the genital tract and urinary tract
Gonococcal uretritis, 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 only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If no clinical improvement is 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 geographically. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.
The single dose of ciprofloxacin is expected to be associated with lower efficacy than with the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections
There are limited data on the efficacy of treating post-surgical intra-abdominal infections.

Travellers' diarrhoea
When selecting ciprofloxacin, consideration should be given to the information on resistance to ciprofloxacin in relevant pathogens for the countries visited.

Infections of the bones and joints
Depending on the results of the microbiological test, ciprofloxacin should be given in combination with other antimicrobial agents.

Inhalation of anthrax pathogens
Recommended use in humans is mainly based on *in vitro* susceptibility tests and animal experimental data, together with limited human data. Treatment should be administered in consideration of the relevant national and/or international guidelines.

Children and adolescents
The official recommendations should be considered when administering ciprofloxacin in children and adolescents. 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.

Studies on growing animals have shown that ciprofloxacin can cause arthropathies in weight-bearing joints. Safety data from a randomised double-blind clinical study on ciprofloxacin administration to children (ciprofloxacin: n = 335, mean age = 6.3 years; control group: n = 349, mean age = 6.2 years; age range = 1 to 17 years), suspected cases of drug-induced arthropathy (based on clinical from joint-related findings) occurred in 7.2% and 4.6% by day +42. The follow-up after one year revealed an incidence of drug-induced arthropathy of 9.0% and. 5.7%. The rise in the frequency of suspected cases of arthropathy was, over time, not statistically significant between the two groups. Due to possible undesirable effects on joints and/or periarticular tissue, ciprofloxacin should be administered only after a careful benefit/risk evaluation.

Bronchopulmonary infections in cystic fibrosis
Children and adolescents aged 5 – 17 years took part in the clinical studies. Only limited experience is available regarding treatment of children aged between 1 and 5 years.

Complicated urinary tract infections and pyelonephritis
Treatment of urinary tract infections with ciprofloxacin should be considered when other treatments cannot be used and should be based on the results of microbiological tests.
Children and adolescents aged 1 – 17 years took part in the clinical studies.

Other specific severe infections
Other severe infections in accordance with official recommendations, or after a careful benefit/risk assessment in cases where conventional therapy cannot be performed or has failed, as well as in cases where, based on the results of microbial tests, the use of ciprofloxacin is justified.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been investigated in clinical studies and the clinical experience is limited. Caution is therefore advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylactic and anaphylactoid reactions, may occur even after a single dose (see section 4.8) and may be life-threatening. In such cases, ciprofloxacin should be discontinued and adequate medical treatment is required.

Musculoskeletal system
Ciprofloxacin should generally not be used in patients with a positive history of tendon disease/complaints that occur in association with quinolone treatment. Nevertheless, in very rare cases, after microbiological confirmation of the causative organism and careful evaluation of the risk/benefit ratio, ciprofloxacin can be prescribed to these patients for the treatment of certain severe infections, especially after failure of standard therapy or in the presence of bacterial resistance, where the microbiological data justify the use of ciprofloxacin.
During treatment with ciprofloxacin, tendinitis and tendon rupture (especially of the Achilles tendon), sometimes bilateral, may occur even within the first 48 hours of starting therapy. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients and in patients concomitantly treated with corticosteroids (see section 4.8).
At the first signs of tendinitis (e. g. painful swelling or inflammation), the treatment with ciprofloxacin must be immediately discontinued and the affected limb should be rested.
Ciprofloxacin should be administered with caution to patients with myasthenia gravis, as the symptoms may be aggravated in individual cases (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to result in photosensitisation. Patients should be advised to avoid prolonged exposure to sunlight or ultraviolet light (solarium) when taking ciprofloxacin (see section 4.8). Treatment should be discontinued if photosensitivity reactions (such as sunburn-like skin reactions) occur.

Central nervous system

Ciprofloxacin like other quinolones are known to be capable of precipitating seizures or lowering the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should therefore be used with caution in patients with disorders of the central nervous system which predispose to seizure. If seizures occur, ciprofloxacin should be discontinued immediately (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/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on observed neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients treated with ciprofloxacin. Treatment with ciprofloxacin should be discontinued in patients who develop neuropathy symptoms, including pain, burning, tingling, light-headedness and/or weakness, in order to prevent the development of irreversible damage (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).

Gastrointestinal tract
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate antibiotic-associated colitis (possibly life-threatening with a fatal outcome), which must be treated immediately (see section 4.8). In such cases, ciprofloxacin should be discontinued immediately and appropriate therapy initiated. Antiperistaltic preparations are contraindicated in this situation.

Renal and lower urinary tract
There have been reports of crystalluria associated with the use of ciprofloxacin (see section 4.8). Patients being treated with ciprofloxacin should therefore drink adequate amounts of fluids. Pronounced alkalinity of the urine should be avoided.

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

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported during the use of ciprofloxacin (see section 4.8). If signs and symptoms of hepatic disease occur (such as anorexia, jaundice, dark urine, pruritus or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported during treatment with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit outweighs the possible risk. In such cases, the potential occurrence of haemolysis should be monitored.

Resistance
During or after treatment with ciprofloxacin, pathogens resistant to ciprofloxacin may be isolated, with or without clinically manifest superinfection. A particular risk for the selection of ciprofloxacin-resistant pathogens exists during prolonged periods of treatment and/or with nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* pathogens.

Cytochrome P450
Ciprofloxacin inhibits CYP 1A2 and may thus lead to increased serum concentrations of concomitantly administered substances that are also metabolised via this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine). Combined administration of ciprofloxacin and tizanidine is contraindicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for signs of overdose and determination of serum concentrations (e.g. theophylline) may be required (see section 4.5).

Methotrexate
Co-administration of ciprofloxacin and methotrexate is not recommended (see section 4.5).

Interactions with laboratory tests
The *in vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* can lead to false-negative bacteriological results in samples from patients currently taking ciprofloxacin.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section 4.8).

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 the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelate complex formation

Concurrent use of ciprofloxacin (oral) with multivalent cation-containing products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, as well as drugs with higher buffer capacity (e. g. didanosine tablets) containing magnesium, aluminium or calcium, reduces resorption of ciprofloxacin. Cipro-Denk 500 should therefore be taken either 1 to 2 hours before or at least 4 hours after taking such medication. This restriction does not apply to antacids of the type H2-receptor blockers.

Food and dairy products

Calcium as part of a meal has only an insignificant effect on absorption of the active substance; however, concomitant ingestion of dairy products or mineral-enriched beverages

(e.g. milk, milk products -such as yoghurt-, calcium-enriched orange juice) and ciprofloxacin should be avoided, as the absorption of ciprofloxacin may be reduced.

Probenecid

Probenecid inhibits the renal excretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases the serum concentration of ciprofloxacin.

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 C_{max} 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 the serum tizanidine concentration (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when ciprofloxacin was co-administered. A potentiated hypotensive and sedative effect is associated with increased serum tizanidine concentrations.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by co-administration of ciprofloxacin and hence lead to increased methotrexate plasma levels; this can increase the risk of methotrexate-related toxic reactions. Concomitant administration is not recommended (see section 4.4).

Theophylline

Concomitant administration of ciprofloxacin and theophylline can lead to undesirable elevated serum concentrations of theophylline. Adverse reactions may be triggered in this way, which in very rare cases may be life-threatening or fatal. During concomitant use, the serum concentrations of theophylline should be monitored and theophylline dose reduced as needed (see section 4.4).

Other xanthine derivatives

Elevated serum levels of xanthine derivates, i.e. caffeine or pentoxiphylline (oxpentifyllin), were detected when administered concurrently with ciprofloxacin.

Phenytoin

The serum level of phenytoin may be increased or decreased when ciprofloxacin and phenytoin are administered concomitantly. Monitoring of plasma levels is therefore

recommended.

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

Vitamin K antagonists

Co-administration of ciprofloxacin and a vitamin K antagonist may enhance the anticoagulant effect. The risk varies depending on the infection present, as well as the patient's age and general condition, so that it is difficult to assess the level of the increase in INR (international normalised ratio) caused by ciprofloxacin.
More frequent INR monitoring is recommended during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione) .

Glibenclamide
In particular cases, concurrent administration of ciprofloxacin and glibenclamide containing medicinal products can intensify the action of glibenclamide (hypoglycaemia).

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

In a clinical study, it was shown that concomitant use of ropinirole and ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isoenzyme, results in a 60% and 84% increase in ropinirole C_{max} and AUC, respectively. Monitoring and appropriate adjustment of the ropinirole dosage are recommended during and shortly after completion of treatment 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

Concomitant administration of 250 mg ciprofloxacin and clozapine for 7 days led to an increase in the serum concentrations of clozapine and N-desmethylclozapine by 29% and 31%, respectively. Clinical monitoring and appropriate adjustment of the clozapine dosage are advised during and shortly after treatment with ciprofloxacin (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Pregnancy
The data available on the use of ciprofloxacin in pregnant women do not indicate malformations or foetal/neonatal toxicity due to ciprofloxacin. Animal studies showed no direct or indirect harmful effects with respect to reproductive toxicity.
In juvenile and prenatal animals, effects on the immature cartilage were observed upon quinolone exposure. Thus, it cannot be excluded that the medicine causes damage to articular cartilage in the immature or juvenile organism/foetus (see section 5.3).
As a precautionary measure, administration of ciprofloxacin during pregnancy should be avoided.

Lactation
Due to the potential risk of articular damage, ciprofloxacin should not be taken during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction skills. Thus, the ability to drive or use machines may be impaired.

4.8 Undesirable effects

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

The adverse drug reactions from clinical studies and post-marketing surveillance of ciprofloxacin (oral, intravenous and sequential therapy) are listed according to the frequency groups below. The frequency analysis takes into account data obtained with oral and intravenous use of ciprofloxacin.

System organ class	**Common** ≥1/100 up to <1/10	**Uncommon** ≥1/1000 up to <1/100	**Rare** ≥1/10000 up to <1/1000	**Very rare** <1/10000	**Frequency not known** (cannot be estimated from the available data)
Infections and infestations		mycotic super-infections	antibiotic-associated colitis (very rarely with a possible fatal outcome) (see section 4.4)		
Blood and lymphatic		eosinophilia	leukocytopenia, anaemia,	haemolytic anaemia,	

System organ class	Common ≥1/100 up to <1/10	Uncommon ≥1/1000 up to <1/100	Rare ≥1/10000 up to <1/1000	Very rare <1/10000	Frequency not known (cannot be estimated from the available data)
system disorders			neutropenia, leukocytosis, thrombocytopenia, thrombocytosis	agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)	
Immune system disorders			Hypersensitivity reactions, allergic oedema / angioedema	Anaphylactic reactions, Anaphylactic shock (life-threatening) (see section 4.4), serum sickness-like reaction	
Metabolism and nutrition disorders		loss of appetite	hyperglycaemia		
Psychiatric disorders		psychomotor hyperactivity / agitation	states of confusion and disorientation, states of anxiety, nightmares, depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4),hallucinations	pathological psychotic behaviour (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4)	
Nervous system disorders		headache, light-headedness, insomnia, disturbed	paraesthesia and dysaesthesia, hypoaesthesia tremor,	migraine, impaired coordination, unsteady gait, olfactory nerve	peripheral neuropathy (see section 4.4)

System organ class	**Common** ≥1/100 up to <1/10	**Uncommon** ≥1/1000 up to <1/100	**Rare** ≥1/10000 up to <1/1000	**Very rare** <1/10000	**Frequency not known** (cannot be estimated from the available data)
		sense of taste and smell	seizures (including status epilepticus) (see section 4.4), dizziness	disorders, intracranial hypertension	
Eye disorders			visual disturbances (e.g. diplopia)	impairment of colour perception	
Ear and labyrinth disorders			tinnitus, hearing loss/ impaired hearing		
Cardiac disorders			tachycardia		ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9).
Vascular disorders			vasodilation, hypotension, syncope	vasculitis	
Respiratory, thoracic and mediastinal disorders			dyspnoea, (including asthmatic conditions)		
Gastrointestinal disorders	nausea diarrhoea	vomiting, gastrointestinal and abdominal pain, dyspepsia, flatulence		pancreatitis	

System organ class	**Common** ≥1/100 up to <1/10	**Uncommon** ≥1/1000 up to <1/100	**Rare** ≥1/10000 up to <1/1000	**Very rare** <1/10000	**Frequency not known** (cannot be estimated from the available data)
Hepatobiliary disorders		rise in transaminase, bilirubin	hepatic dysfunction, cholestasis, hepatitis	liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and subcutaneous tissue disorders		rashes, itchiness, urticaria	sensitivity to light (see section 4.4)	petechia, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		musculoskeletal pain (e.g. pain in the extremities, back pain, chest pain), joint pain	myalgia, arthritis, increased muscle tension and muscle cramps	myasthenia, tendinitis tendon rupture (primarily Achilles tendon) (see section 4.4), aggravation of symptoms of myasthenia gravis (see section 4.4), muscle pain and vaginal synovitis (tendovaginitis)	
Renal and urinary disorders		renal dysfunction	renal failure, haematuria, crystalluria (see section 4.4), tubulointerstitial nephritis		

System organ class	Common ≥1/100 up to <1/10	Uncommon ≥1/1000 up to <1/100	Rare ≥1/10000 up to <1/1000	Very rare <1/10000	Frequency not known (cannot be estimated from the available data)
General disorders and Administration site conditions		asthenia, fever	oedema, perspiration (hyperhidrosis)		
Investigations		elevation of blood alkaline phosphatase	abnormal prothrombin values, increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

Paediatric patients
The above-mentioned incidence of arthropathies relates to data collected in studies on adults. It has been reported that arthropathy commonly occurs (see section 4.4).

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

4.9 Overdose

The toxicity symptoms of an overdose with 12 g were described as slight.
An acute overdose of 16 g caused acute renal failure.
Symptoms of an overdose are: Dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal complaints, impaired liver and kidney function, crystalluria and haematuria. Reversible renal damage has been observed.

In addition to routine emergency procedures, e.g. gastric emptying followed by medical carbon, it is recommended that renal function be monitored, including urinary pH determination, together with acidification if necessary, to minimise the risk of crystalluria. Adequate hydration must be maintained. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.
Only a small amount of ciprofloxacin (<10%) is eliminated by means of haemodialysis or peritoneal dialysis.

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

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones.
ATC-Code: J01MA02

Mechanism of action:

As a fluoroquinolone antibiotic, ciprofloxacin has a bactericidal effect based on inhibition of topoisomerase II (DNA-gyrase) and topoisomerase IV. Both enzymes are needed for bacterial DNA replication, transcription, recombination and repair.

PK/PD relationships:

Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for bacterial pathogens and the relation between the area under the curve (AUC) and the minimum inhibitory concentration.

Resistance mechanism:

In-vitro studies have shown that resistance to ciprofloxacin is triggered by mutations in the bacterial topoisomerase as a rule, and it usually develops slowly and gradually ("multiple step" type). The degree of cross-resistance that results between ciprofloxacin and other fluoroquinolones is variable. Individual mutations do not usually lead to clinically relevant resistance, while multiple mutations do generally lead to clinically relevant resistances to many or all antibiotics from the class of quinolones. Impermeability of the bacterial cell wall and/or resistance due to efflux pump activity may have a variable effect on the degree of susceptibility to quinolones. This depends on the physical/chemical properties of each active substance within its class, as well as on affinity to the transport system. All *in vitro* resistance mechanisms are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics, such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms, can influence susceptibility against ciprofloxacin. Plasmid-mediated resistance, encoded by qnr genes, has been reported.

Antibacterial spectrum of efficacy:

The prevalence of acquired resistances can vary for certain species with regard to geographical and temporal aspects. Knowledge of the local resistance patterns is therefore of importance, particularly in the treatment of severe infections.
If, due to the local resistance status, the use of substance seems questionable for at least some forms of infection, expert advice should be sought.
Grouping of relevant pathogens, based on their susceptibility to ciprofloxacin (for streptococcal pathogens, see section 4.4).

Commonly susceptible species

Aerobic Gram-positive microorganisms

Bacillus anthracis

Staphylococcus saprophyticus

Aerobic Gram-negative microorganisms

Enterobacter aerogenes

Enterobacter cloacae

Haemophilus influenzae

Moraxella catarrhalis

Morganella morganii

Neisseria meningitidis

Proteus vulgaris

Salmonella enterica (incl. *S. typhi/paratyphi*)

Serratia marcescens

Shigella spp.

Other microorganisms

Chlamydia trachomatis

Chlamydophila pneumoniae

Legionella pneumophila

Mycoplasma hominis

Mycoplasma pneumoniae

Species in which acquired resistance may pose a problem during use

Aerobic Gram-positive microorganisms

Enterococcus faecalis

Staphylococcus aureus (methicillin-sensitive)

Staphylococcus aureus (methicillin-resistant)

Staphylococcus epidermidis

Staphylococcus haemolyticus

Staphylococcus hominis

Aerobic Gram-negative microorganisms

Acinetobacter baumannii

Burkholderia cepacia

Campylobacter jejuni

Citrobacter freundii

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Neisseria gonorrhoeae

Proteus mirabilis

Pseudomonas aeruginosa

Inherently resistant species

Aerobic Gram-positive microorganisms

Enterococcus faecium

Aerobic Gram-negative microorganisms

Stenotrophomonas maltophilia

Anaerobic microorganisms

Bacteroides spp.

Clostridium difficile

Other microorganisms

Treponema pallidum

Ureaplasma urealyticum

5.2 Pharmacokinetic properties

Absorption

After oral administration of single doses of 250 mg, 500 mg and 750 mg ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations after 1-2 hours.

Single doses of 100-750 mg produced dose-dependent peak serum concentrations (C_{max}) between 0.56 and 3.7 mg/l. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70-80 %.

It has been shown that an oral dose of 500 mg every 12 hours leads to an area under the serum concentration-time curve (AUC) equivalent to that after intravenous infusion of 400 mg ciprofloxacin, administered over 60 minutes every 12 hours.

Distribution

The protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is primarily found in non-ionised form in the blood plasma and has a huge distribution volume at steady-state of 2-3 l/kg body weight. Ciprofloxacin reaches high concentrations in certain body fluids and tissues like lung tissue (epithelial fluid, alveolar macrophages, biopsy tissue), paranasal 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 were found, which were identified as: desethylene ciprofloxacin (M1), sulfociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). The metabolites exhibit an antibacterial effect in vitro, but which is considerably lower than that of the parent substance.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 isoenzyme.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a lesser degree, via the faeces. The serum elimination half-life in patients with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (in % of ciprofloxacin dose)		
	oral use	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M1 – M4)	11.3	7.5

Renal clearance is between 180-300 ml/kg/h and the total body clearance is 480-600 ml/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. A severely impaired renal function leads to a prolonged serum elimination half-life of up to 12 hours.

Non-renal clearance of ciprofloxacin mainly takes place via active transintestinal secretion and metabolism. 1% of the dose is excreted via the bile. Ciprofloxacin is present in the bile at high concentrations.

Paediatric patients

Only limited data are available on pharmacokinetics in paediatric patients.
In a study with children (over 1 year of age), no age-dependency was established for C_{max} and AUC. On multiple dosing (10 mg/kg three times daily), no relevant increase in C_{max} and AUC occurred.

After a 1-hour intravenous infusion of 10 mg/kg in 10 children with severe sepsis below 1 year of age, C_{max} was 6.1 mg/l (range 4.6-8.3 mg/l), whilst in comparison, C_{max} was 7.2 mg/l (range 4.7-11.8 mg/l) in children aged 1-5 years. 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 above-mentioned age groups.

These values are within the range established for adults at equivalent therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, a half-life of about 4-5 hours was calculated and bioavailability of the oral suspension is about 50 to 80%.

5.3 Preclinical safety data

Preclinical 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 many other quinolones, ciprofloxacin is phototoxic in animals at clinical relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or photocarcinogenic effect of ciprofloxacin *in vitro* and in animal trials. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
Like other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in juvenile animals. The extent of cartilage damage varies depending on age, experimental animal species and dose; cartilage damage is reduced by taking the weight off the joints. Studies with mature animals (rat, dog) showed no damage to cartilage. In a study with young beagle dogs, ciprofloxacin caused severe articular damage at therapeutic doses after two weeks of treatment, which could still be seen after 5 months.

6. Pharmaceutical particulars

6.1 List of excipients

Sodium starch glycolate, low-substituted hydroxy-propyl cellulose, magnesium stearate (Ph.Eur.) [vegetable], hypromellose, macrogol 400, titanium dioxide (E 171), talc

6.2 Incompatibilities

Not known

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30 ºC.
Do not use after the expiry date.
Keep out of reach and sight of children.

6.5 Nature and contents of container

Individual packages with 10 film-coated tablets and a leaflet.

6.6 Special precautions for disposal

No special requirements.

7. Marketing authorisation holder

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München, Germany

8. Marketing authorisation number in Germany

50427.02.00

9. Date of first registration / Date of renewal of the marketing authorisation in Germany

21.05.2003 / 11.11.2009

10. Date of revision of the text

08/2015

11. Prescription status

Prescription only medicine.