

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2mg/ml, Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each presentation of Ciprofloxacin 2mg/ml infusion contains the following:

Ciprofloxacin 100 mg/50 ml, Solution for Infusion

1 ml of Solution for Infusion contains 2mg Ciprofloxacin as 2.544mg Ciprofloxacin lactate.

Each 50 ml vial contains 100 mg Ciprofloxacin (as Ciprofloxacin Lactate).

Excipient: Each 50ml contains 7.7 mmol (177 mg) Sodium.

Ciprofloxacin 200 mg/100 ml, Solution for Infusion

1 ml of Solution for Infusion contains 2mg Ciprofloxacin as 2.544mg Ciprofloxacin lactate

Each 100 ml vial contains 200 mg Ciprofloxacin. (as Ciprofloxacin Lactate).

Excipient: Each 100ml contains 15.4 mmol (354 mg) Sodium.

Ciprofloxacin 400 mg/200 ml, Solution for Infusion

1 ml of Solution for Infusion contains 2mg Ciprofloxacin as 2.544mg Ciprofloxacin lactate.

Each 200 ml bottle contains 400 mg Ciprofloxacin. (as Ciprofloxacin Lactate).

Excipient: Each 200 ml contains 30.8 mmol (708 mg) Sodium.

For a 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

Ciprofloxacin is indicated for the treatment of serious and/or life-threatening infections caused by ciprofloxacin-susceptible pathogens. The following indications can be considered for treatment with Ciprofloxacin when oral therapy is not possible or not reliable:

- complicated urinary tract infections
- infections of the lower respiratory tract including pneumonia caused by aerobic gram-negative bacteria, in case of Streptococcus pneumoniae infections ciprofloxacin is not the substance of first choice.
- complicated skin and soft tissue infections
- osteomyelitis

Children and adolescents:

Ciprofloxacin may be used for 2nd and 3rd line treatment of complicated urinary tract infections and pyelonephritis in children and adolescents of 1-17 years of age and for the treatment of acute pulmonary exacerbation of cystic fibrosis associated with Pseudomonas aeruginosa in children

and adolescents of 5-17 years of age. The use of ciprofloxacin in paediatric patients with complicated urinary tract infections and pyelonephritis should be restricted to infections caused by organisms for which ciprofloxacin is the drug of choice, based on the results of antimicrobial susceptibility testing. Treatment should be initiated by a physician who is experienced in the treatment of severe infections in children and adolescents and after careful benefit/risk evaluation, due to possible adverse events related to joints and / or surrounding tissues (see sections 4.4 and 5.1)

In case of mixed infections with anaerobes ciprofloxacin must be combined with other antibiotics effective against anaerobes.

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

4.2 Posology and method of administration

The solution for infusion should be administered over an infusion period of 60 minutes. Due to the increased risk of local reactions, higher intravenous doses in particular should only be administered via a large vein or a central line. Mixing with other solutions: see sections 6.2 and 6.6.

The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings. Generally, acute and chronic infections (e.g. osteomyelitis and prostatitis, etc), where the causative organism is known to be sensitive to ciprofloxacin, should be treated for at least three days after the signs and symptoms of the infection have disappeared.

Adults:

The adult dosage is 200 – 400 mg ciprofloxacin twice daily.

In case of very serious, life-threatening or recurrent infections the dosage can be increased to 400 mg three times daily. The maximum daily dose is 1200 mg.

Osteomyelitis:

Prior to initiation of therapy, bacteriological sensitivity tests should be conducted. As with all other antibiotics, the patient should be monitored during therapy for the development of resistant strains of initially sensitive bacteria, especially *P. aeruginosa* and *S. aureus* (see the relevant statements in section 5.1). Average duration of treatment can be 4-6 weeks. If a prolonged treatment is necessary, a reassessment of treatment should be done at 2 months at the latest.

Impaired renal function:

In patients with a creatinine clearance in the range 31 – 60 ml/minute/1.73 m² or a serum creatinine concentration in the range 124 – 174 µmol/l, the maximum daily intravenous dose is 800 mg.

If creatinine clearance is ≤ 30 ml/minute/1.73 m² or the serum creatinine concentration is ≥ 175 µmol/l, the maximum daily intravenous dose is 400 mg.

In patients on haemodialysis or CAPD, the maximum daily intravenous dose is also 400 mg. On the dialysis days, the dose is given after the haemodialysis session.

Impaired hepatic function:

In case of impaired hepatic function it is not necessary to adjust the dosage.

Impaired renal and hepatic function:

Dose adjustment according to renal function. Monitoring the level of active substance in the blood provides the most reliable basis for dose adjustment.

Elderly:

Due to the higher plasma levels in the elderly it is advisable to administer doses based on creatinine clearance and severity of disease.

Paediatric patients:

Acute lower respiratory tract infections caused by *Pseudomonas aeruginosa* in children and adolescents (5-17years) with cystic fibrosis:

Twice daily intravenous administration of 15 mg/kg bodyweight, or 10 mg/kg bodyweight three times daily (maximum of 1200 mg per day).

Complicated urinary tract infections and pyelonephritis:

For complicated urinary tract infections or pyelonephritis the dose is 6 to 10 mg/kg IV every 8 hours with a maximum of 400 mg per dose or 10 to 20 mg/kg orally every 12 hours with a maximum of 750 mg per dose.

For complicated urinary tract infections or pyelonephritis the duration of treatment is 10-21 days. The dosage in children with impaired renal and/or hepatic function has not been investigated.

4.3 Contraindications

Ciprofloxacin is contraindicated in:

- patients with a hypersensitivity to ciprofloxacin, chinolin carboxylic acid derivatives or to any of the excipients
- children under 5 years of age. With regard to the safety and use of ciprofloxacin in children, see also section 4.4
- Children and growing adolescents except for the treatment of acute pulmonary exacerbations of cystic fibrosis in children aged 5 to 17 years.
- pregnancy and lactation
- patients with a history of tendon disorder related to fluoroquinolone administration
- Concurrent administration of ciprofloxacin and tizanidine

4.4 Special warnings and precautions for use

Renal and urinary system:

Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatic disorders:

Cases of hepatic necrosis up to 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.

Blood and lymphatic system:

Patients with a family history of or actual defects in glucose-6-phosphate dehydrogenase activity are prone to haemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.

Central nervous system:

As with other fluoroquinolones, specific undesirable effects with regard to the central nervous system must be taken into account when using Ciprofloxacin. In patients with epilepsy or other lesions of the central nervous system (e.g. reduced convulsion threshold, a history of epileptic seizures, diminished cerebral blood flow, changes in brain structure or stroke), ciprofloxacin is only to be used after carefully weighing the benefits against the risk, because the possibility of central nervous side effects puts these patients at increased risk.

The undesirable effects sometimes occur already after the first administration of ciprofloxacin. Depression or psychoses lead to self-endangering behaviour in some cases. If such reactions occur, treatment with ciprofloxacin must be discontinued immediately and the treating physician informed.

Cardiac disorders:

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

Pediatric use:

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

The use of ciprofloxacin for indications other than the treatment of acute pulmonary exacerbation of cystic fibrosis caused by *P. aeruginosa* infection (children aged 5 – 17 years), complicated urinary tract infections and pyelonephritis (children aged 1 – 17 years) and for the use in inhalational anthrax (post-exposure) has not been evaluated in clinical trials and the clinical experience is limited. The use of ciprofloxacin should follow the official guidance.

Gastrointestinal tract:

When during or after the treatment with ciprofloxacin or another fluoroquinolone severe and persistent diarrhoea occurs, pseudomembranous colitis must be taken into account (life-threatening with possibly fatal outcome). In that case the ciprofloxacin therapy must immediately be discontinued and an appropriate treatment initiated. Antiperistaltics are contraindicated. The transaminase or alkaline phosphatase concentrations may temporarily increase or cholestatic icterus might occur, especially in patients with previous liver damage.

Musculoskeletal system:

If there is any indication of tendinitis (e.g. painful swelling) the administration of ciprofloxacin or other fluoroquinolones must immediately be discontinued, the affected extremity should not be strained and a physician must be consulted. Very rarely, a partial or total rupture (in particular of the Achilles tendon) has been reported, especially in elderly patients who were previously treated systemically with glucocorticoids.

Ciprofloxacin may cause an exacerbation of Myasthenia gravis symptoms. Therefore, in case of any symptom indicating an exacerbation of Myasthenia gravis a physician must be consulted.

Photosensitivity:

Ciprofloxacin and other fluoroquinolones may cause photosensitivity. Therefore, it is recommended to avoid prolonged exposure to sunlight or UV light during treatment with ciprofloxacin. However, if this is not possible the patient is recommended to use a sun-protection cream. When photosensitivity occurs the treatment must be discontinued.

Hypersensitivity:

Hypersensitivity reactions and allergic reactions occurred in some cases after the first administration of ciprofloxacin. If such reactions occur, a physician must immediately be consulted.

Anaphylactic/anaphylactoid reactions can in very rare cases develop into life-threatening shock, sometimes even after the first administration of ciprofloxacin. In that case, the ciprofloxacin treatment must be discontinued, and medical treatment for shock should be given.

Local reaction:

Local reactions have been reported after intravenous administration of ciprofloxacin. These reactions occur more frequently when the infusion time is 30 minutes or less. These may be manifested as local skin reactions, which rapidly disappear after the infusion has been completed. Further intravenous administration is not contraindicated unless the reactions reoccur or worsen. Because ciprofloxacin has some activity against *Mycobacterium tuberculosis*, false-negative cultures may occur when the specimens are obtained during ciprofloxacin treatment.

Ciprofloxacin contains 15.4 mmol (354 mg) sodium per 100 ml solution for infusion. This has to be taken into consideration for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Probenecid

Probenecid inhibits the renal excretion of ciprofloxacin resulting in an increase in the plasma concentration of ciprofloxacin.

CYP1A2

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, tacrine, ropinirol, tizanidine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose. Determination of serum concentrations, especially of theophylline, and dose adjustments may be necessary. The interaction between theophylline and ciprofloxacin is potentially life-threatening.

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.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This may increase the risk of methotrexate associated toxic reactions. Therefore, patients receiving methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Ciclosporin

Following concomitant administration of ciprofloxacin and ciclosporin a transient increase of the serum creatinine concentration has been observed in separate cases. Therefore, the serum creatinine concentration must be checked regularly (twice per week) in these patients.

Oral anticoagulants (e.g. warfarin)

Ciprofloxacin, like other quinolones, may enhance the effect of coumarin derivatives including warfarin. In the case of concomitant administration of these products, prothrombin time (PT) or other suitable coagulation tests should be monitored. If necessary, the oral anticoagulant dose should be adjusted as appropriate.

Glibenclamide

When used simultaneously, ciprofloxacin may, in certain cases, increase the effect of glibenclamide (hypoglycaemia).

NSAIDs

Animal trials have shown that the concurrent administration of very high doses of fluoroquinolones and certain NSAIDs (but not acetylsalicylic acid) may provoke convulsions.

Mexiletine

Simultaneous administration of ciprofloxacin and mexiletine can lead to increased plasma concentrations of mexiletine.

4.6 Pregnancy and lactation

Pregnancy

Use during pregnancy is contraindicated. There are limited data on the use of ciprofloxacin during pregnancy. Up to now, no evidence has been found of an increased risk of congenital abnormalities or other undesirable effects following use of ciprofloxacin or other quinolones during the first trimester. Teratogenic effects have not been observed in animal experimental research. In juvenile and prenatal animals exposed to quinolones effects on immature cartilage have been observed. Since the risks for humans are unknown Ciprofloxacin must not be administered during pregnancy (see section 4.3).

Lactation

Ciprofloxacin is excreted in breast milk. Due to the risk of arthropathy and other potentially severe toxicity in the infant, ciprofloxacin is contraindicated during lactation (see section 4.3).

4.7 Effects on ability to drive and use machines

Ciprofloxacin has minor or moderate influence on the ability to drive and use machines. When undesirable effects on the central nervous system, like dizziness, occur, it is prohibited to drive a vehicle or to operate machines.

4.8 Undesirable effects

Adverse reactions have been reported in 5-14% of patients receiving ciprofloxacin. Most frequent adverse reactions involve the gastro-intestinal tract and the central nervous system.

The following adverse reactions have been observed:

In this section undesirable effects are defined as follows:

very common	($\geq 1/10$)
common	($\geq 1/100$ to $< 1/10$)
uncommon	($\geq 1/1,000$ to $< 1/100$)
rare	($\geq 1/10,000$ to $< 1/1,000$)
very rare	($< 1/10,000$), not known (cannot be estimated from the available data)

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Infections and infestations:

Uncommon: moniliasis

Blood and the lymphatic system disorders:

Uncommon: eosinophilia, leukopenia.

Rare: leukopenia (granulocytopaenia), anaemia, leukocytosis, altered prothrombin values, thrombocytopenia, thrombocytaemia (thrombocytosis).

Very rare: haemolytic anaemia, pancytopenia, agranulocytosis.

Immune system disorders:

Rare: oedema (peripheral, angio, facial), allergic reaction, drug fever, anaphylactoid (anaphylactic) reaction.

Very rare: pulmonary oedema in case of shock (anaphylactic; life-threatening), itching rash, serum sickness-like symptoms.

Metabolism and nutrition disorders:

Rare: hyperglycaemia.

Psychiatric disorders:

Rare: anxiety, nightmares, depression, hallucinations.

Very rare: psychotic reactions.

Nervous system disorders:

Common: perverted sensation of taste, dizziness, headache, insomnia, agitation, confusion.

Rare: taste loss (reduced taste), paraesthesia (peripheral paralgesia), tremor (shaking), convulsions, migraine.

Very rare: parosmia (impaired smell), anosmia (usually reversible after interruption), grand mal convulsion, abnormal (unstable) gait, intracranial hypertension.

Eye disorders:

Rare: disturbed vision, diplopia, chromatopsia.

Ear and labyrinth disorders:

Rare: tinnitus, transient hearing loss (particularly high frequencies).

Cardiac disorders:

Rare: tachycardia.

In very rare cases ventricular arrhythmia, QT interval prolongation and torsades de pointes have been reported. These events were observed predominantly among patients with further risk factors for QTc prolongation.

Vascular disorders:

Uncommon: (thrombo)phlebitis.

Rare: syncope (fainting), vasodilation (heat stress).

Very rare: vasculitis (petechiae, hemorrhagic bullae, papules, crust formation).

Respiratory, thoracic and mediastinal disorders:

Rare: dyspnoea, laryngeal oedema.

Gastrointestinal disorders:

Common: nausea, diarrhoea.

Uncommon: vomiting, dyspepsia, flatulence, anorexia, abdominal pain.

Rare: pseudomembranous colitis, moniliasis (oral).

Very rare: moniliasis (gastro-intestinal), pancreatitis.

Hepato-biliary disorders:

Rare: icterus, cholestatic icterus.

Very rare: hepatitis, liver cell necrosis (very rarely resulting in life-threatening liver function failure).

Skin and subcutaneous tissue disorders:

Common: rash.

Uncommon: pruritis, papillo-macular rash, urticaria.

Rare: photosensitivity.

Very rare: erythema nodosum, erythema multiforme (minor), Stevens-Johnson syndrome, epidermal necrolysis (Lyell Syndrome).

Musculoskeletal, connective tissue and bone disorders:

Uncommon: arthralgia (joint pain).

Common: arthropathy (in children – see also section 4.4)

Rare: myalgia (muscular pain), joint disorder (swollen joints).

Very rare: tendinitis (in particular of the Achilles tendon), partial or total tendon ruptures (in particular of the Achilles tendon), aggravation of the symptoms of myasthenia.

Renal and urinary disorders:

Rare: acute renal failure, impaired renal function, vaginal moniliasis, haematuria, crystalluria, interstitial nephritis.

General disorders and administration site conditions:

Uncommon: asthenia (general sensation of weakness, fatigue), injection site reactions.

Rare: transpiration.

Investigations:

Uncommon: increase of blood creatinine levels, increased blood urea; abnormal liver function test results (increased SGOT and SGPT), bilirubinemia and increased alkaline phosphatase.

Very rare: increment of amylase/lipase levels.

4.9 Overdose

In acute and extreme overdosage, reversible kidney damage is seen. An overdose of 12 g has been reported to lead to mild symptoms of toxicity. Symptoms of overdose may include dizziness, tremor, headaches, tiredness, seizures, hallucinations, confusion, gastrointestinal upset, liver and kidney abnormalities, crystalluria, haematuria.

The patient should be monitored closely and treated symptomatically with supportive measures. Adequate hydration must be ensured. At haemodialysis or peritoneal dialysis only a modest amount of ciprofloxacin (less than 10%) is eliminated.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quinolone antibacterials (ATC code: J01MA02)

Mode of action:

Ciprofloxacin is effective in vitro against a large number of Gram-negative aerobic bacteria including *P. aeruginosa*. It is also effective against Gram-positive organisms, such as staphylococci and streptococci. Anaerobes are generally less sensitive. Ciprofloxacin has a rapid

bactericidal effect, both in the growth phase and in the rest phase. During the growth phase of bacteria, a partial rolling up and unfolding of chromosomes takes place. The enzyme DNA-gyrase plays a crucial role in this process. Ciprofloxacin inhibits DNA-gyrase, resulting in inhibition of DNA synthesis.

Mechanism of resistance:

Resistance to ciprofloxacin develops in stages through genomic mutations (multiple-step type). Transferable plasmid-mediated quinolone resistance associated with qnr has been detected in quinolone-resistant clinical strains of E.coli and Klebsiella spp. As a result of its mechanism of action, ciprofloxacin does not show cross-resistance with other important, chemically different groups of substances such as beta-lactam antibiotics, aminoglycosides, tetracyclines, macrolides and polypeptides, sulphonamides, trimethoprim and nitrofurantoin.

Within the class of quinolones cross-resistance has been observed. Development of resistance to ciprofloxacin and other fluoroquinolones has been observed in staphylococci, especially methicillin-resistant S. aureus, P. aeruginosa, E.coli and E. faecalis (see the sensitivity table). Especially patients undergoing long-term treatment (e.g. in cystic fibrosis, osteomyelitis), or patients who are extremely susceptible to infections (e.g. in selective prophylaxis in certain groups of neutropenic patients, artificial ventilation) show the highest risk. The percentage of resistant strains can be subject to great local variation. Regular determination of resistance is therefore recommended.

Breakpoints:

According to EUCAST the following breakpoints for aerobic bacteria have been defined for ciprofloxacin:

- Enterobacteriaceae: ≤0.5 µg/ml for susceptible, >1 µg/ml for resistant;
- Pseudomonas spp. ≤0.5 µg/ml for susceptible, >1 µg/ml for resistant;
- Acinetobacter spp. ≤1 µg/ml for susceptible, >1 µg/ml for resistant;
- S. pneumoniae ≤0.125 µg/ml for susceptible, >2 µg/ml for resistant;
- Staphylococcus spp. ≤1 µg/ml for susceptible, >1 µg/ml for resistant;
- H. influenzae and M. catarrhalis ≤0.5 µg/ml for susceptible, >0.5 µg/ml for resistant;
- Neisseria gonorrhoeae: ≤0.03 µg/ml for susceptible, >0.06 µg/ml for resistant;
- N. meningitidis: ≤0.03 µg/ml for susceptible, >0.06 µg/ml for resistant;
- Non-species related breakpoints are ≤0.5 µg/ml for susceptible, and >1 µg/ml for resistant organisms.

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.

Commonly susceptible species
Gram-positive species
Bacillus anthracis
Gram-negative aerobe species
Citrobacter spp.
Citrobacter freundii
Enterobacter cloacae
Haemophilus influenzae
Moraxella spp.
Moraxella catarrhalis

Morganella spp.
Morganella morganii
Proteus spp.
Proteus mirabilis
Proteus vulgaris
Salmonella spp.
Serratia liquefaciens
Serratia marcescens
Shigella spp.
Shigella flexneri
Shigella sonnei
Species for which acquired resistance may be a problem
Gram-positive aerobes
Coagulase-negative Staphylococcus
Enterococcus faecalis
MRSA*
Staphylococcus aureus
Staphylococcus aureus (methicillin susceptible)
Streptococcus spp.
Streptococcus agalactiae
Streptococcus pneumoniae
S. pneumoniae PEN-R
Streptococcus pyogenes
Gram-negative aerobes
Acinetobacter spp.
Acinetobacter baumannii
Campylobacter spp.
Campylobacter jejuni
Enterobacter spp.
Enterobacter aerogenes
Enterobacter spp. Amp-C producing
Escherichia coli
E. coli ESBL producing
Klebsiella pneumoniae
Klebsiella oxytoca
Klebsiella pneumoniae ESBL producing
Neisseria gonorrhoeae

Pseudomonas aeruginosa
Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Gram-negative aerobes
E. coli multi-resistant
Providencia spp.
Stenotrophomonas maltophilia
Other pathogens
Ureaplasma urealyticum
Anaerobes
Bacteroides fragilis

* MRSA are very likely to be resistant to ciprofloxacin and ciprofloxacin should not be used to treat presumed or known MRSA infections unless the organism is known to be susceptible.

Abbreviations:

ESBL: Extended Spectrum Beta-lactamases

MRSA: Methicillin-resistant Staphylococcus aureus

Other information:

A study on Rhesus-monkeys that were exposed to anthrax by inhalation revealed that 8/9 animals survived the experiment when these animals were treated from 1 day after anthrax exposure with ciprofloxacin twice daily for a period of 30 days. The MIC of the Bacillus anthrax strain that was applied in this study was 0.08 µg/ml. Because the MIC₉₀ for ciprofloxacin of 70 other Bacillus anthrax strains varied between 0.03-0.06 µg/ml, it seems likely that ciprofloxacin would also be effective in other strains than the one that was applied in this study. There are however no sufficient clinical data available to draw conclusion about the effectiveness of ciprofloxacin in the treatment of anthrax in humans. Physicians are recommended to follow current national and/or international consensus documents regarding the treatment of anthrax.

5.2 Pharmacokinetic properties

Absorption:

Ciprofloxacin is rapidly and effectively absorbed after oral administration. The peak plasma concentration is reached 0.5 - 2 hours after taking 50 - 1000 mg p.o. and varies from 0.3 - 5.9 mg/l. There is a linear correlation between dose on the one hand and plasma concentration and AUC on the other. The bioavailability of ciprofloxacin after oral administration is between 70 % and 85 %.

The bioavailability is lower if antacids that contain aluminium and/or magnesium hydroxide, and calcium and iron salts are used concomitantly.

No accumulation occurs on repeated administration (twice daily). Twelve hours after i.v. administration of 200 mg the plasma concentration is still higher than the MIC values of the majority of clinically relevant pathogens (approximately 0.1 µg/ml).

Distribution:

In steady-state conditions the apparent distribution volume of ciprofloxacin is situated between 1,7 and 2,7 l/kg. This relatively high distribution volume indicates an effective tissue and fluid penetration. This applies to gall, kidney, gall bladder and liver tissue.

Concentrations in pulmonary tissue, gynaecological tissue and prostate tissue and fluid were also significantly higher than the serum concentration.

The ciprofloxacin concentration in blister fluid, lymph, nasal secretion, peritoneal fluid, saliva and fatty tissue is approximately half of the serum concentration. The ciprofloxacin concentration in the sputum consists of 50-70% of the serum concentration.

Animal experiments have shown that ciprofloxacin passes the placenta and is excreted in breast milk.

The plasma protein binding of ciprofloxacin is situated between 16% and 28% and is not dependent on the concentration and pH (determined by means of ultrafiltration).

Biotransformation:

Ciprofloxacin is mainly excreted unchanged. Part of it is converted into desethylene-, sulpho-, oxo- and formylciprofloxacin. All metabolites are active, but in a lesser degree than ciprofloxacin.

Elimination:

After oral administration ciprofloxacin is excreted unchanged for approx. 70% and after i.v. administration for approx. 77%. After oral administration 45% is excreted unchanged in the urine and 25% is excreted in the faeces. After i.v. administration 62% is excreted unchanged in the urine and 15% is excreted in the faeces. After oral administration 19% and after i.v. administration 12% of ciprofloxacin is excreted in the urine and faeces in the form of metabolites. A larger number of metabolites after oral administration indicates some degree of first-pass metabolism, mainly forming sulphociprofloxacin.

The total body clearance of ciprofloxacin is independent of the dose and remains unchanged in case of multiple administration. The renal clearance constitutes 60%-70% of the total body clearance and is approximately 3 times higher than the creatinine clearance. The renal clearance occurs through glomerular filtration and active tubular secretion.

The elimination half-life of ciprofloxacin after single or multiple oral dosage is between 3,4 and 6,9 hours. After single and multiple i.v. dosage the elimination half-life is between 3 – 4,6 hours.

Characteristics in patients:

In patients with severely impaired renal function (creatinine clearance <30 ml/min) the elimination half-life may be prolonged by a factor of 2.

The elimination half-life of ciprofloxacin does not change with age.

The pharmacokinetics of ciprofloxacin in children with cystic fibrosis differs from that in children without cystic fibrosis, and dosing recommendations are only applicable for children with cystic fibrosis. Oral administration of 20 mg/kg twice daily to children with cystic fibrosis gives an exposure that is comparable to that in adults following an oral dose of 750 mg twice daily.

Children:

The data available to substantiate the pharmacokinetic data in children 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, less than 1 year of age C_{max} was 6.1 mg/L (range 4.6 – 8.3 mg/L) after a 1-

hour intravenous infusion at a dose level of 10 mg/kg; and 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 pediatric 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

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.

Ciprofloxacin is potentially neurotoxic and causes reversible defects of the testes in case of higher dosage. Mutagenicity of ciprofloxacin has not been indicated in mutagenicity studies. However, like a number of other quinolones ciprofloxacin is phototoxic in animals in exposure values relevant to humans. The phototoxic, photomutagenic and photocarcinogenic potential of ciprofloxacin is comparable to that of other gyrase inhibitors. Other preclinical effects were observed only at exposures that were sufficiently in excess of the maximum human exposure so that concern for human safety is negligible.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic Acid
Sodium Chloride
Hydrochloric Acid for pH adjustment
Water for Injections

6.2 Incompatibilities

Ciprofloxacin 2mg/ml infusion is incompatible with injection solutions (e.g. penicillins, heparin solutions), which are chemically or physically unstable at its pH of 3.9-4.5.

Unless compatibility is proven, the infusion should always be administered separately.

For compatible co-infusion solutions see Section 6.6.

6.3 Shelf life

3 years

After first opening:

Single dose container. Use immediately after first opening.

After dilution:

Use within 42 hours if diluted with the administration fluids.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.
Keep vial/bottle in outer carton in order to protect from light.

6.5 Nature and contents of container

Type II clear glass, internally siliconised, colourless bottles with a siliconised grey bromobutyl rubber stopper, containing 50ml, 100ml or 200ml of Ciprofloxacin 2mg/ml Infusion.

Pack size: Individual vial / bottle in unit carton.

6.6 Special precautions for disposal

The solution should be inspected visually for particulate matter or discoloration prior to administration. The solution should only be used if clear and free from particles.

Ciprofloxacin 2mg/ml infusion has been shown to be compatible with Ringer's solution, 0.9% sodium chloride solution, 5% and 10% glucose solutions, glucose/saline and fructose 10% solution.

The product should not be mixed with other drug products which are chemically or physically unstable at its pH of 3.9-4.5 (see Section 6.2)

The product should be infused directly and administered over 30 -60 minutes. The 200ml dose (400mg) dose should be infused over 60 minutes.

For single use only. Any unused product or waste material should be disposed of in accordance with local requirements, immediately after use.

7 MARKETING AUTHORISATION HOLDER

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Crewe
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8 MARKETING AUTHORISATION NUMBER(S)

PL 20568/0003

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