

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin Niche 2mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of solution for infusion contains ciprofloxacin (as lactate) equivalent to 2 mg ciprofloxacin.

Each glass bottle with 50 ml solution for infusion contains 100 mg ciprofloxacin (as lactate). The sodium content is 177mg (7.7 mmol).

Each glass bottle with 100 ml solution for infusion contains 200 mg ciprofloxacin (as lactate). The sodium content is 354mg (15.4 mmol).

Each glass bottle with 200 ml solution for infusion contains 400 mg ciprofloxacin (as lactate). The sodium content is 708mg (30.8 mmol).

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Solution for infusion.

Clear yellowish to slightly yellow, odourless solution free from foreign bodies.

The pH-value of the solution for infusion ranges from 3.9 to 4.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ciprofloxacin solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1) Special attention should be paid to available information on resistance to ciprofloxacin before 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
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *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
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents:

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

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are 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

The dosage is determined by the indication, the severity and the site of infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and in children and adolescents, the body weight.

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

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of the physician. IV treatment should be followed by oral route as soon as possible.

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

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

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

Adults

| Indications | | Daily dose in mg | Total duration of treatment (including switch to oral therapy as soon as possible) |
|---|---|--|---|
| Infections of the lower respiratory tract | | 400 mg twice daily to 400 mg three times a day | 7 to 14 days |
| Infections of the upper respiratory tract | Acute exacerbation of chronic sinusitis | 400 mg twice daily to 400 mg three times a day | 7 to 14 days |
| | Chronic suppurative otitis media | 400 mg twice daily to 400 mg three times a day | 7 to 14 days |

| | | | |
|--|--|--|--|
| | Malignant external otitis | 400 mg three times a day | 28 days up to 3 months |
| Urinary tract infections | Complicated and Uncomplicated pyelonephritis | 400 mg twice daily to 400 mg three times a day | 7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses) |
| | Prostatitis | 400 mg twice daily to 400 mg three times a day | 2 to 4 weeks (acute) |
| Genital tract infections | Epididymo-orchitis and pelvic inflammatory diseases | 400 mg twice daily to 400 mg three times a day | at least 14 days |
| Infections of the gastro-intestinal tract and intraabdominal infections | Diarrhoea caused by bacterial pathogens including <i>Shigella</i> spp. other than <i>Shigella dysenteriae</i> type 1 and empirical treatment of severe travellers' diarrhoea | 400 mg twice daily | 1 day |
| | Diarrhoea caused by <i>Shigella dysenteriae</i> type 1 | 400 mg twice daily | 5 days |
| | Diarrhoea caused by <i>Vibrio cholerae</i> | 400 mg twice daily | 3 days |
| | Typhoid fever | 400 mg twice daily | 7 days |
| | Intra-abdominal infections due to Gram-negative bacteria | 400 mg twice daily to 400 mg three times a day | 5 to 14 days |
| Infections of the skin and soft tissue | | 400 mg twice daily to 400 mg three times a day | 7 to 14 days |
| Bone and joint infections | | 400 mg twice daily to 400 mg three times a day | max. of 3 months |
| 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 | | 400 mg twice daily to 400 mg three times a day | Therapy should be continued over the entire period of neutropenia |
| Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment. Drug administration should begin as soon as possible after suspected or confirmed exposure. | | 400 mg twice daily | 60 days from the confirmation of <i>Bacillus anthracis</i> exposure |

Children and adolescents

| Indications | Daily dose in mg | Total duration of treatment (including switch to oral therapy as soon as possible) |
|--|--|--|
| Cystic fibrosis | 10 mg/kg body weight three times a day with a maximum of 400 mg per dose. | 10 to 14 days |
| Complicated urinary tract infections and pyelonephritis | 6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose. | 10 to 21 days |
| Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment 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 400 mg per dose. | 60 days from the confirmation of <i>Bacillus anthracis</i> exposure |

| | | |
|-------------------------|---|-------------------------------------|
| Other severe infections | 10 mg/kg body weight three times a day with a maximum of 400 mg per dose. | According to the type of infections |
|-------------------------|---|-------------------------------------|

Geriatric patients

Geriatric 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 m ²] | Serum creatinine [μmol/L] | Intravenous Dose [mg] |
|---|------------------------------|--|
| >60 | <124 | See usual dosage |
| 30-60 | 124 to 168 | 200-400 mg every 12 h |
| <30 | >169 | 200-400 mg every 24 h |
| Patients on haemodialysis | >169 | 200-400 mg every 24 h (after dialysis) |
| Patients on peritoneal dialysis | >169 | 200-400 mg every 24 h |

In patients with impaired liver function no adjustment of dosage is necessary.

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

Method of administration

Ciprofloxacin should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.

In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin and 30 minutes for 200 mg Ciprofloxacin 2mg/ml solution for infusion. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.

The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

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 useSevere 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 coadministered with other appropriate antibacterial agents.

Streptococcal Infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections

Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*.

Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

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.

Children and adolescents

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.

Broncho-pulmonary infections in cystic fibrosis

Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

Complicated urinary tract infections and pyelonephritis

Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.

Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections

Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.

The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity

Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

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 Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).

At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.

Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

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

Quinolones are known to trigger seizures or lower the seizure threshold. 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 selfendangering behaviour. In these 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 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 antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- elderly
- cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)

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

Gastrointestinal System

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

Renal and urinary system

Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

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, ropinirole, tizanidine). 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

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

Interaction with tests

The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Injection Site Reaction

Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

NaCl Load

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on Ciprofloxacin**Probenecid**

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

Effects of Ciprofloxacin on other medicinal products:Tizanidine

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

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced undesirable 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.

Oral anticoagulants

Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant 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 an oral anticoagulant agent.

Ropinirole

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

Clozapine

Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylozapine were increased by 29% and 31%, respectively.

Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised (see section 4.4).

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).

4.6 Fertility, pregnancy and lactation**Pregnancy**

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or fetoneonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animal 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.

Lactation

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

4.7 Effects on ability to drive and use machines

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.8 Undesirable effects

The most commonly reported adverse drug reactions (ADRs) are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, and injection and infusion site reactions.

ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin (oral, intravenous and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

| System Organ Class | Common ≥1/100 to <1/10 | Uncommon ≥1/1,000 to <1/100 | Rare ≥ 1/10,000 to < 1/1,000 | Very Rare <1/10,000 | Frequency not known (cannot be estimated from available data) |
|------------------------------------|-------------------------------------|--|---|-------------------------------|---|
| Infections and Infestations | | Mycotic superinfections | Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4) | | |
| Blood and | | Eosinophilia | Leukopenia | Haemolytic | |

| | | | | | |
|--|--|---|---|--|--|
| Lymphatic System Disorders | | | Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytæmia | anaemia Agranulocytosis Pancytopenia (lifethreatening) Bone marrow depression (lifethreatening) | |
| Immune System Disorders | | | Allergic reaction Allergic oedema / angiooedema | Anaphylactic reaction Anaphylactic shock (lifethreatening) (see section 4.4) Serum sicknesslike reaction | |
| Metabolism and Nutrition Disorders | | Anorexia | Hyperglycaemia | | |
| Psychiatric Disorders | | Psychomotor hyperactivity / agitation | Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations | Psychotic reactions (see section 4.4) | |
| Nervous System Disorders | | Headache Dizziness Sleep disorders Taste disorders | Par- and Dysaesthesia Hypoesthesia Tremor Seizures (see section 4.4) Vertigo | Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension | Peripheral neuropathy (see section 4.4) |
| 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 pains Dyspepsia Flatulence | | Pancreatitis | |
| 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 lifethreatening) Toxic epidermal necrolysis (potentially lifethreatening) | |
| 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 myasthenia gravis (see section 4.4) | |
| Renal and Urinary Disorders | | Renal impairment | Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis | | |
| General Disorders and Administration Site Conditions | Injection and infusion site reactions (only intravenous administration) | Asthenia Fever | Oedema Sweating (hyperhidrosis) | | |
| Investigations | | Increase in blood alkaline phosphatase | Prothrombin level abnormal Increased amylase | | |

The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

| | |
|----------|---|
| Common | Vomiting, Transient increase in transaminases, Rash |
| Uncommon | Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- |

| | |
|------|---|
| | and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema |
| Rare | Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture |

Paediatric patients

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).

4.9 Overdose

An overdose of 12g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16g has been reported to cause acute renal failure.

Symptoms of overdose may include 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 also 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

Pharmacotherapeutic group: fluoroquinolones

ATC Code: J01 MA 02

Mechanism of action:

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:

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

Mechanism of resistance:

In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmid-mediated resistance encoded by *qnr*-genes has been reported.

Spectrum of antibacterial activity:

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

| Microorganisms | Susceptible | Resistant |
|---|----------------------------|-------------------------|
| <i>Enterobacteria</i> | $S \leq 0.5 \text{ mg/L}$ | $R > 1 \text{ mg/L}$ |
| <i>Pseudomonas</i> | $S \leq 0.5 \text{ mg/L}$ | $R > 1 \text{ mg/L}$ |
| <i>Acinetobacter</i> | $S \leq 1 \text{ mg/L}$ | $R > 1 \text{ mg/L}$ |
| <i>Staphylococcus</i> spp. ¹ | $S \leq 1 \text{ mg/L}$ | $R > 1 \text{ mg/L}$ |
| <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> | $S \leq 0.5 \text{ mg/L}$ | $R > 0.5 \text{ mg/L}$ |
| <i>Neisseria gonorrhoeae</i> | $S \leq 0.03 \text{ mg/L}$ | $R > 0.06 \text{ mg/L}$ |
| <i>Neisseria meningitidis</i> | $S \leq 0.03 \text{ mg/L}$ | $R > 0.06 \text{ mg/L}$ |
| Non-species-related breakpoints* | $S \leq 0.5 \text{ mg/L}$ | $R > 1 \text{ mg/L}$ |

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

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

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

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

| COMMONLY SUSCEPTIBLE SPECIES |
|--|
| <u>Aerobic Gram-positive micro-organisms</u> <i>Bacillus anthracis</i> (1) |
| <u>Aerobic Gram-negative micro-organisms</u> <i>Aeromonas</i> spp. <i>Brucella</i> spp. <i>Citrobacter koseri</i> <i>Francisella tularensis</i> <i>Haemophilus ducreyi</i> <i>Haemophilus influenzae</i> * <i>Legionella</i> spp. <i>Moraxella catarrhalis</i> * <i>Neisseria meningitidis</i> <i>Pasteurella</i> spp. <i>Salmonella</i> spp.* <i>Shigella</i> spp.* <i>Vibrio</i> spp. <i>Yersinia pestis</i> |
| <u>Anaerobic micro-organisms</u> <i>Mobiluncus</i> |
| <u>Other micro-organisms</u> <i>Chlamydia trachomatis</i> (\$) <i>Chlamydia pneumoniae</i> (\$) <i>Mycoplasma hominis</i> (\$) <i>Mycoplasma pneumoniae</i> (\$) |
| SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM |
| <u>Aerobic Gram-positive micro-organisms</u> <i>Enterococcus faecalis</i> (\$) <i>Staphylococcus</i> spp.*(2) |
| <u>Aerobic Gram-negative micro-organisms</u> <i>Acinetobacter baumannii</i> + <i>Burkholderia cepacia</i> +* |

Campylobacter spp.+*
*Citrobacter freundii**
Enterobacter aerogenes
Enterobacter cloacae *
*Escherichia coli**
Klebsiella oxytoca
*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**

Anaerobic micro-organisms

Peptostreptococcus spp.
Propionibacterium acnes

INHERENTLY RESISTANT ORGANISMS

Aerobic Gram-positive micro-organisms

Actinomyces
Enterococcus faecium
Listeria monocytogenes

Aerobic Gram-negative micro-organisms

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Excepted as listed above

Other micro-organisms

Mycoplasma genitalium
Ureaplasma urealyticum

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

+ Resistance rate \geq 50% in one or more EU countries

(\$): Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax.

(2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display *in-vitro* antimicrobial activity but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally.

| Excretion of ciprofloxacin (% of dose) | | |
|---|-----------------------------------|---------------|
| | Intravenous administration | |
| | Urine | Faeces |
| Ciprofloxacin | 61.5 | 15.2 |
| Metabolites (M ₁ -M ₄) | 9.5 | 2.6 |

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic Acid (90%)
Sodium Chloride
Hydrochloric acid 1N (for pH-adjustment only)
Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. The following active substances or solution for dilution should not be administered simultaneously, e.g.: Penicillins, Heparin solutions, which are chemically and physically unstable at the pH of Ciprofloxacin 2mg/ml (pH 3.9-4.5).

6.3 Shelf life

3 years.
Once opened use immediately.
Once diluted: Chemical and physical in-use stability has been demonstrated for 4 hours at 25°C.
From the microbiological point of view, the product should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Keep the container in the outer carton in order to protect from light.
For storage conditions of diluted product, see section 6.3.

6.5 Nature and contents of container

Transparent Type I glass vial with rubber stopper and aluminium cap

Pack sizes:

1 vial with 50 ml/100 ml/200 ml contains 100 mg/200mg/400 mg of Ciprofloxacin (as lactate).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Ciprofloxacin 2mg/ml solution for infusion is compatible with Ringer lactate solution, , 0.9% sodium chloride solution, 5% and 10% glucose solutions, and 5% and 10% fructose solutions. When ciprofloxacin infusion solutions are mixed with compatible infusion solutions, for microbial reasons and light sensitivity these solutions must be administered shortly after mixture.

As the infusion solution is sensitive to light, only remove the bottles from the folding box for use. In daylight the full efficacy of the solution is guaranteed over a period of 3 days.

For single use only.

If product is inadvertently refrigerated, crystals may form. Do not use if crystals are present. These crystals will, however, redissolve at room temperature and do not adversely affect the quality of this product.

The (diluted) solution should be inspected visually for particulate matter and discoloration prior to administration. Only clear and colourless or slightly coloured solution should be used.

7 MARKETING AUTHORISATION HOLDER

Niche Generics Limited
1 The Cam Centre
Wilbury Way
Hitchin
Herts
SG4 0TW
United Kingdom

8 MARKETING AUTHORISATION NUMBER

PA 1063/37/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 14th March 2008

Date of last renewal: 22nd March 2010

10 DATE OF REVISION OF THE TEXT

November 2011