

**Public Assessment Report**  
**Decentralised Procedure**

**CIPROFLOXACIN 2MG/ML SOLUTION FOR INFUSION**

**UK/H/1443/001/DC**  
**UK Licence No: PL 19364/0032**

**UKR REGULATORY AFFAIRS LIMITED**

## **LAY SUMMARY**

On 13<sup>th</sup> February 2009, the UK granted UKR Regulatory Affairs Limited Marketing Authorisations (licences) for the medicine Ciprofloxacin 2 mg/ml Solution for Infusion

Ciprofloxacin 2 mg/ml Solution for Infusion is an antibiotic belonging to the fluoroquinolone family. Ciprofloxacin works by killing specific strains of bacteria that cause infections. Ciprofloxacin 2 mg/ml Solution for Infusion is used to treat a range of bacterial infections in children, adolescents and adults.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of using Ciprofloxacin 2 mg/ml Solution for Infusion outweigh the risks; hence a Marketing Authorisation has been granted.

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## Module 1

|                                     |   |
|-------------------------------------|---|
| <b>Product Name</b>                 | Ciprofloxacin 2mg/ml Solution for Infusion  |
| <b>Type of Application</b>          | Generic, Article 10.1   |
| <b>Active Substance</b>             | Ciprofloxacin   |
| <b>Form</b>                         | Solution for Infusion   |
| <b>Strength</b>                     | 2mg/ml  |
| <b>MA Holder</b>                    | UKR Regulatory Affairs Limited<br>First Floor, Chiltern House, Thame Road<br>Haddenham, Buckinghamshire, HP17 8BY |
| <b>Reference Member State (RMS)</b> | UK  |
| <b>CMS</b>                          | Belgium, Germany, Italy, The Netherlands and Spain  |
| <b>Procedure Number</b>             | UK/H/1443/001/DC  |
| <b>End of Procedure</b>             | Day 210 – 1 <sup>st</sup> February 2009   |

## Module 2

# Summary of Product Characteristics

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2mg/ml Solution for infusion

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg ciprofloxacin (as ciprofloxacin lactate) in 5 % w/v glucose monohydrate solution.

Each bag with 100 ml contains 200 mg ciprofloxacin

Each bag with 200 ml contains 400 mg ciprofloxacin

Excipient: Glucose (see section 4.4)

For a full list of excipients, see Section 6.1.

#### 3 PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless solution.

pH is 4.00-4.50

Osmolality is 260-300mOsmol/L

#### 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 the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.

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

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 intra-abdominal 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   |

| Indications   | Daily dose in mg   | Total duration of treatment (including switch to oral therapy as soon as possible) |              |
|---|--|--|--------------|
|   | 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<br>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<br>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*

| Indication  | 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<br>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 <sup>2</sup> ] | 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 dose adjustment is required.  
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 /.../. 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 use**

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal Infections (including *Streptococcus pneumoniae*)

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

Genital tract infections

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

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

#### 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.

#### Glucose Load

Ciprofloxacin /.../ solution for infusion contains 5 g glucose in 100 mL solution for infusion. This should be taken into account in patients with diabetes mellitus.

## **4.5 Interaction with other medicinal products and other forms of interaction**

### Effects of other medicinal products on ciprofloxacin:

#### Probenecid

Probenecid interferes with 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 a potentiated hypotensive and sedative effect.

#### Methotrexate

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

#### Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

#### Other xanthine derivatives

On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

#### Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

#### 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 co-administration with ciprofloxacin are advised (see section 4.4).

### **4.6 Pregnancy and lactation**

#### Pregnancy

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

#### 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.

| <b>System Organ Class</b>                   | <b>Common<br/>≥ 1/100 to &lt;<br/>1/10</b> | <b>Uncommon<br/>≥ 1/1 000 to &lt;<br/>1/100</b>             | <b>Rare<br/>≥ 1/10 000 to &lt; 1/1<br/>000</b>  | <b>Very Rare<br/>&lt; 1/10 000</b>  | <b>Frequency<br/>not known<br/>(cannot be<br/>estimated<br/>from<br/>available<br/>data)</b> |
|---|--|---|---|---|--|
| <b>Infections and Infestations</b>          |  | Mycotic superinfections                                     | Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)           |   |  |
| <b>Blood and Lymphatic System Disorders</b> |  | Eosinophilia  | Leukopenia<br>Anaemia<br>Neutropenia<br>Leukocytosis<br>Thrombocytopenia<br>Thrombocytæmia          | Haemolytic anaemia<br>Agranulocytosis<br>Pancytopenia (life-threatening)<br>Bone marrow depression (life-threatening) |  |
| <b>Immune System Disorders</b>              |  |   | Allergic reaction<br>Allergic oedema / angiooedema  | Anaphylactic reaction<br>Anaphylactic shock (life-threatening) (see section 4.4)<br>Serum sickness-like reaction      |  |
| <b>Metabolism and Nutrition Disorders</b>   |  | Anorexia  | Hyperglycaemia  |   |  |
| <b>Psychiatric Disorders</b>                |  | Psychomotor hyperactivity / agitation                       | Confusion and disorientation<br>Anxiety reaction<br>Abnormal dreams<br>Depression<br>Hallucinations | Psychotic reactions (see section 4.4)   |  |
| <b>Nervous System Disorders</b>             |  | Headache<br>Dizziness<br>Sleep disorders<br>Taste disorders | Par- and Dysaesthesia<br>Hypoaesthesia<br>Tremor<br>Seizures (see section 4.4)<br>Vertigo           | Migraine<br>Disturbed coordination<br>Gait disturbance<br>Olfactory nerve disorders<br>Intracranial hypertension      | Peripheral neuropathy (see section 4.4)  |
| <b>Eye Disorders</b>                        |  |   | Visual disturbances   | Visual colour distortions   |  |
| <b>Ear and Labyrinth Disorders</b>          |  |   | Tinnitus<br>Hearing loss / Hearing impaired   |   |  |

| <b>System Organ Class</b>                                    | Common<br>≥ 1/100 to < 1/10 | Uncommon<br>≥ 1/1 000 to < 1/100  | Rare<br>≥ 1/10 000 to < 1/1 000                            | Very Rare<br>< 1/10 000  | <b>Frequency not known</b><br>(cannot be estimated from available data) |
|--|-----------------------------|---|--|--|---|
| <b>Cardiac Disorders</b>                                     |                             |   | Tachycardia  |  | Ventricular arrhythmia, QT prolongation, torsades de pointes *          |
| <b>Vascular Disorders</b>                                    |                             |   | Vasodilatation<br>Hypotension<br>Syncope                   | Vasculitis   |   |
| <b>Respiratory, Thoracic and Mediastinal Disorders</b>       |                             |   | Dyspnoea (including asthmatic condition)                   |  |   |
| <b>Gastrointestinal Disorders</b>                            | Nausea<br>Diarrhoea         | Vomiting<br>Gastrointestinal and abdominal pains<br>Dyspepsia<br>Flatulence     |  | Pancreatitis   |   |
| <b>Hepatobiliary Disorders</b>                               |                             | Increase in transaminases<br>Increased bilirubin                                | Hepatic impairment<br>Cholestatic icterus<br>Hepatitis     | Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)   |   |
| <b>Skin and Subcutaneous Tissue Disorders</b>                |                             | Rash<br>Pruritus<br>Urticaria   | Photosensitivity reactions (see section 4.4)               | Petechiae<br>Erythema multiforme<br>Erythema nodosum<br>Stevens-Johnson syndrome (potentially life-threatening)<br>Toxic epidermal necrolysis (potentially life-threatening) |   |
| <b>Musculoskeletal, Connective Tissue and Bone Disorders</b> |                             | Musculoskeletal pain (e.g. extremity pain, back pain, chest pain)<br>Arthralgia | Myalgia<br>Arthritis<br>Increased muscle tone and cramping | Muscular weakness<br>Tendinitis<br>Tendon rupture (predominantly Achilles tendon) (see section 4.4)<br>Exacerbation of symptoms of myasthenia gravis (see section 4.4)       |   |

| System Organ Class  | Common<br>≥ 1/100 to < 1/10   | Uncommon<br>≥ 1/1 000 to < 1/100       | Rare<br>≥ 1/10 000 to < 1/1 000   | Very Rare<br>< 1/10 000 | Frequency not known<br>(cannot be estimated from available data) |
|---|---|--|---|-------------------------|--|
| <b>Renal and Urinary Disorders</b>                          |   | Renal impairment                       | Renal failure<br>Haematuria<br>Crystalluria (see section 4.4)<br>Tubulointerstitial nephritis |                         |  |
| <b>General Disorders and Administration Site Conditions</b> | Injection and infusion site reactions (only intravenous administration) | Asthenia<br>Fever                      | Oedema<br>Sweating (hyperhidrosis)  |                         |  |
| <b>Investigations</b>                                       |   | Increase in blood alkaline phosphatase | Prothrombin level abnormal<br>Increased amylase   |                         |  |

\*These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

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

|          |  |
|----------|--|
| Common   | Vomiting, Transient increase in transaminases, Rash  |
| Uncommon | Thrombocytopenia, 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 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

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

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:

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

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

| <b>Microorganisms</b>   | <b>Susceptible</b> | <b>Resistant</b> |
|---|--------------------|------------------|
| Enterobacteria  | S ≤ 0.5 mg/L       | R > 1 mg/L       |
| <i>Pseudomonas</i>  | S ≤ 0.5 mg/L       | R > 1 mg/L       |
| <i>Acinetobacter</i>  | S ≤ 1 mg/L         | R > 1 mg/L       |
| <i>Staphylococcus</i> spp. <sup>1</sup>                           | S ≤ 1 mg/L         | R > 1 mg/L       |
| <i>Haemophilus influenzae</i> and<br><i>Moraxella catarrhalis</i> | S ≤ 0.5 mg/L       | R > 0.5 mg/L     |
| <i>Neisseria gonorrhoeae</i>                                      | S ≤ 0.03 mg/L      | R > 0.06 mg/L    |
| <i>Neisseria meningitidis</i>                                     | S ≤ 0.03 mg/L      | R > 0.06 mg/L    |
| Non-species-related breakpoints*                                  | S ≤ 0.5 mg/L       | R > 1 mg/L       |

<sup>1</sup> *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)

| <b>COMMONLY SUSCEPTIBLE SPECIES</b>   |
|---|
| <u>Aerobic Gram-positive micro-organisms</u><br><i>Bacillus anthracis</i> (1)   |
| <u>Aerobic Gram-negative micro-organisms</u><br><i>Aeromonas</i> spp.<br><i>Brucella</i> spp.<br><i>Citrobacter koseri</i><br><i>Francisella tularensis</i><br><i>Haemophilus ducreyi</i><br><i>Haemophilus influenzae</i> *<br><i>Legionella</i> spp.<br><i>Moraxella catarrhalis</i> *<br><i>Neisseria meningitidis</i><br><i>Pasteurella</i> spp.<br><i>Salmonella</i> spp.*<br><i>Shigella</i> spp.*<br><i>Vibrio</i> spp.<br><i>Yersinia pestis</i>  |
| <u>Anaerobic micro-organisms</u><br><i>Mobiluncus</i>   |
| <u>Other micro-organisms</u><br><i>Chlamydia trachomatis</i> (\$)<br><i>Chlamydia pneumoniae</i> (\$)<br><i>Mycoplasma hominis</i> (\$)<br><i>Mycoplasma pneumoniae</i> (\$)  |
| <b>SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM</b>   |
| <u>Aerobic Gram-positive micro-organisms</u><br><i>Enterococcus faecalis</i> (\$)<br><i>Staphylococcus</i> spp. *(2)  |
| <u>Aerobic Gram-negative micro-organisms</u><br><i>Acinetobacter baumannii</i> <sup>+</sup><br><i>Burkholderia cepacia</i> <sup>+</sup> *<br><i>Campylobacter</i> spp. <sup>+</sup> *<br><i>Citrobacter freundii</i> *<br><i>Enterobacter aerogenes</i><br><i>Enterobacter cloacae</i> *<br><i>Escherichia coli</i> *<br><i>Klebsiella oxytoca</i><br><i>Klebsiella pneumoniae</i> *<br><i>Morganella morganii</i> *<br><i>Neisseria gonorrhoeae</i> *<br><i>Proteus mirabilis</i> *<br><i>Proteus vulgaris</i> *<br><i>Providencia</i> spp.<br><i>Pseudomonas aeruginosa</i> *<br><i>Pseudomonas fluorescens</i><br><i>Serratia marcescens</i> * |
| <u>Anaerobic micro-organisms</u><br><i>Peptostreptococcus</i> spp.<br><i>Propionibacterium acnes</i>  |



| <b>INHERENTLY RESISTANT ORGANISMS</b>  |   |
|--|---|
| <u>Aerobic Gram-positive micro-organisms</u><br><i>Actinomyces</i><br><i>Enterococcus faecium</i><br><i>Listeria monocytogenes</i> |   |
| <u>Aerobic Gram-negative micro-organisms</u><br><i>Stenotrophomonas maltophilia</i>  |   |
| <u>Anaerobic micro-organisms</u><br>Excepted as listed above   |   |
| <u>Other micro-organisms</u><br><i>Mycoplasma genitalium</i><br><i>Ureaplasma urealiticum</i>                                      |   |
| *  | 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 <i>Bacillus anthracis</i> 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 <i>in-vitro</i> 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 <i>S. aureus</i> 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 <sub>1</sub> -M <sub>4</sub> ) | 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<sub>max</sub> and AUC were not age-dependent (above one year of age). No notable increase in C<sub>max</sub> and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C<sub>max</sub> 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  
Glucose monohydrate  
Hydrochloric acid (for pH adjustment)  
Water for injections

**6.2 Incompatibilities**

Ciprofloxacin 2mg/ml Solution for infusion is incompatible with injection solutions (e.g. penicillins, heparin solutions) that are chemically or physically unstable at its pH of 4.0-4.5. 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

This product is for single use only and should be used immediately after removal from the overpouch.

**6.4 Special precautions for storage**

Store in the original container to protect from light.

**6.5 Nature and contents of container**

This medicinal product is supplied in a flexible plasticised PVC (polyvinylchloride) bag. Two bag sizes are available: 100 ml and 200 ml. Each infusion bag is overpouched with a PET metal/PE black film.

Pack sizes:

1 x 100 ml

10 x 100 ml

1 x 200 ml

10 x 200 ml

(Not all pack sizes may be marketed.)

**6.6 Special precautions for disposal**

The solution should be visually inspected for particulate matter and discoloration prior to administration. Only clear and colourless solution should be used.

The product should not be mixed with other drug products which are chemically or physically unstable at its pH of 4.0-4.5 (see Section 6.2). However, Ciprofloxacin 2mg/ml Solution for infusion has been shown to be compatible with Ringer's solution, Ringer's lactate solution, 0.9% sodium chloride solution, 5% and 10% glucose solutions, 5% and 10% fructose solutions, glucose/saline solutions.

Unless compatibility is proven, the infusion solution should always be administered separately. In addition, discard any unused portion of product immediately after use.

Any unused product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

UKR Regulatory Affairs Ltd

Chiltern House

Thame Road

Haddenham

Buckinghamshire HP17 8BY

UK

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 19364/0032

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

13/02/2009

**10 DATE OF REVISION OF THE TEXT**

13/02/2009

## Module 3

*The Patient Information Leaflet (PIL) below is the leaflet text agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.*

### PACKAGE LEAFLET : INFORMATION FOR THE USER

#### Ciprofloxacin 2mg/ml Solution for infusion

**Read all of this leaflet carefully before you are given this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

**In this leaflet:**

1. What Ciprofloxacin 2 mg/ml Solution for infusion is and what it is used for
2. Before you are given Ciprofloxacin 2 mg/ml Solution for infusion
3. How to use Ciprofloxacin 2 mg/ml Solution for infusion
4. Possible side effects
5. How to store Ciprofloxacin 2 mg/ml Solution for infusion
6. Further information

#### 1. WHAT CIPROFLOXACIN 2MG/ML SOLUTION FOR INFUSION IS AND WHAT IT IS USED FOR

Ciprofloxacin 2 mg/ml Solution for infusion is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

##### Adults

Ciprofloxacin 2 mg/ml Solution for infusion is used in adults to treat the following bacterial infections:

- respiratory tract infections
- long lasting or recurring ear or sinus infections
- urinary tract infections
- infections of the testicles
- genital organ infections in women
- gastro-intestinal tract infections and intra-abdominal infections
- skin and soft tissue infections
- bone and joint infections
- to treat infections in patients with a very low white blood cell count (neutropenia)
- to prevent infections in patients with a very low white blood cell count (neutropenia)
- anthrax inhalation exposure

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin 2 mg/ml Solution for infusion.

##### Children and adolescents

Ciprofloxacin 2 mg/ml Solution for infusion is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:

- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin 2 mg/ml Solution for infusion may also be used to treat other specific severe infections in children and adolescents when your doctor considered this necessary.

## 2. BEFORE YOU ARE GIVEN CIPROFLOXACIN 2MG/ML SOLUTION FOR INFUSION

**You must not be given Ciprofloxacin 2 mg/ml Solution for infusion if you are:**

- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin 2 mg/ml Solution for infusion (see section 6)
- taking tizanidine (see Section 2: Taking other medicines)

### Take special care with Ciprofloxacin 2 mg/ml Solution for infusion

#### Before you are given Ciprofloxacin 2 mg/ml Solution for infusion

Tell your doctor if you:

- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin 2 mg/ml Solution for infusion
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrhythmias)

#### While under treatment with Ciprofloxacin 2 mg/ml Solution for infusion

Tell your doctor immediately, if any of the following occurs **during treatment with Ciprofloxacin 2 mg/ml Solution for infusion**. Your doctor will decide whether treatment with Ciprofloxacin 2 mg/ml Solution for infusion needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin 2 mg/ml Solution for infusion will have to be stopped.**
- **Pain and swelling in the joints, and tendinitis** may occur occasionally, particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin 2 mg/ml Solution for infusion will have to be stopped, rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.
- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin 2 mg/ml Solution for infusion and contact your doctor immediately.
- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or **psychosis**, your symptoms may become worse under treatment with Ciprofloxacin 2 mg/ml Solution for infusion. If this happens, stop taking Ciprofloxacin 2 mg/ml Solution for infusion and contact your doctor immediately.
- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin 2 mg/ml Solution for infusion and contact your doctor immediately.
- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin 2 mg/ml Solution for infusion, or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus tell your doctor immediately. Ciprofloxacin 2 mg/ml Solution for infusion treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.
- Tell the doctor or laboratory staff that you are taking Ciprofloxacin 2 mg/ml Solution for infusion if you have to provide a **blood or urine sample**.
- Ciprofloxacin 2 mg/ml Solution for infusion may cause **liver damage**. If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin 2 mg/ml Solution for infusion must be stopped immediately.

- Ciprofloxacin 2 mg/ml Solution for infusion may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased**. If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.
- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anemia with ciprofloxacin.
- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin 2 mg/ml Solution for infusion. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

### Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

**Do not use Ciprofloxacin 2 mg/ml Solution for infusion together with tizanidine**, because this may cause side effects such as low blood pressure and sleepiness (see Section 2: "**You must not be given Ciprofloxacin 2 mg/ml Solution for infusion if you are**").

The following medicines are known to interact with Ciprofloxacin 2 mg/ml Solution for infusion in your body. Using Ciprofloxacin 2 mg/ml Solution for infusion together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

### Tell your doctor if you are taking:

- warfarin or other oral anti-coagulants (to thin the blood)
- probenecid (for gout)
- methotrexate (for certain types of cancer, psoriasis, rheumatoid arthritis)
- theophylline (for breathing problems)
- tizanidine (for muscle spasticity in multiple sclerosis)
- clozapine (an antipsychotic)
- ropinirole (for Parkinson's disease)
- phenytoin (for epilepsy)

Ciprofloxacin 2 mg/ml Solution for infusion may **increase** the levels of the following medicines in your blood:

- pentoxifylline (for circulatory disorders)
- caffeine

### Taking Ciprofloxacin 2 mg/ml Solution for infusion with food and drink

Food and drink does not affect your treatment with Ciprofloxacin 2 mg/ml Solution for infusion.

### Pregnancy and breast-feeding

It is preferable to avoid the use of Ciprofloxacin 2 mg/ml Solution for infusion during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin 2 mg/ml Solution for infusion during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

### Driving and using machines

Ciprofloxacin 2 mg/ml Solution for infusion may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin 2 mg/ml Solution for infusion before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

### Important information about some of the ingredients of Ciprofloxacin 2mg/ml Solution for infusion

If you are diabetic please take into account that:

- 100 ml of Ciprofloxacin 2mg/ml Solution for infusion contains 5 g of glucose, and
- 200ml of Ciprofloxacin 2mg/ml Solution for infusion contains 10 g of glucose.

### 3. HOW TO USE CIPROFLOXACIN 2MG/ML SOLUTION FOR INFUSION

Your doctor will explain to you exactly how much Ciprofloxacin 2 mg/ml Solution for infusion you will be given as well as how often and for how long. This will depend on the type of infection you have and how bad it is.

Tell your doctor if you suffer from kidney problems because your dose may need to be adjusted.

Treatment usually lasts between 5 and 21 days, but may be longer for severe infections.

Your doctor will give you each dose by slow infusion through a vein into your bloodstream. For children, the infusion duration is 60 minutes. In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin 2 mg/ml Solution for infusion and 30 minutes for 200 mg Ciprofloxacin 2 mg/ml Solution for infusion. Administering the infusion slowly helps prevent immediate side effects occurring.

Remember to drink plenty of fluids while you are taking Ciprofloxacin 2 mg/ml Solution for infusion.

#### If you stop your course of Ciprofloxacin 2 mg/ml Solution for infusion

- It is important that you **finish the course of treatment** even if you begin to feel better after a few days. If you stop using this medicine too soon your infection may not be completely cured and the symptoms of the infection may return or get worse. You might also develop resistance to the antibiotic.

If you have any more questions about the use of this product, ask your doctor or pharmacist.

### 4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin 2 mg/ml Solution for infusion can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, tell your doctor or pharmacist.

**Common side effects** (between 1 and 10 in every 100 people are likely to get these):

- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

**Uncommon side effects** (between 1 and 10 in every 1,000 people are likely to get these):

- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood clotting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

**Rare side effects** (between 1 and 10 in every 10,000 people are likely to get these):

- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angiooedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- increased blood sugar (hyperglycemia)

- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion), small, pin-point bleeding under the skin (petechiae)
- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles tendon) (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion), urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothrombin) increased levels of the enzyme amylase

**Very rare side effects** (less than 1 in every 10,000 people are likely to get these):

- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis )
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin 2 mg/ml Solution for infusion)

**Frequency not known** (cannot be estimated from the available data)

- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

## **5. HOW TO STORE CIPROFLOXACIN 2MG/ML SOLUTION FOR INFUSION**

Store in the original container in order to protect from light.

This product is for single use only and should be used immediately after removal from the overpouch.

Keep out of the reach and sight of children.

Do not use Ciprofloxacin 2 mg/ml Solution for infusion after the expiry date which is stated on the carton after "EXP": The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

## **6. FURTHER INFORMATION**

### **What Ciprofloxacin 2 mg/ml Solution for infusion contains**

- The active substance is ciprofloxacin
- The other ingredients are lactic acid, glucose monohydrate, hydrochloric acid (0.1N) and water for injections.

### **What Ciprofloxacin 2 mg/ml Solution for infusion looks like and contents of the pack**

Solution for infusion

Your medicinal product is a clear, colourless solution and comes in a 100ml or 200ml PVC bag in packs of 1 or 10.

### **Marketing Authorisation Holder and Manufacturer**

[See Annex I - To be completed nationally]

{Name and address}

{tel}

{fax}

{e-mail}



**This medicinal product is authorised in the Member States of the EEA under the following names:**

This medicinal product is authorised in the Member States of the EEA under the following names:

|                     |  |
|---------------------|--|
| <i>UK :</i>         | Ciprofloxacin 2mg/ml Solution for infusion   |
| <i>Belgium:</i>     | Ciprofloxacin UKR Regulatory Affaires 2mg/ml Oplossing voor intraveneuze infusie, Solution pour perfusion, Infusionslösung |
| <i>Germany:</i>     | Ciprofloxacin UKR 2 mg/ml Infusionslösung  |
| <i>Spain :</i>      | Ciprofloxacino UKR 2mg/ml solución para perfusión EFG  |
| <i>Italy :</i>      | Ciprofloxacina UKR Regulatory Affairs 2mg/ml Soluzione per infusione   |
| <i>Netherlands:</i> | Ciprofloxacin UKR 2mg/ml Solution for infusion   |

**This leaflet was last approved in {MM/YYYY}**

[To be completed nationally]

**Advice/medical education**

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.

If your doctor has prescribed antibiotics, you need them precisely for your current illness.

Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.

Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:

- dosage
- schedules
- duration of treatment

**Consequently, to preserve the efficacy of this drug:**

- 1 - Use antibiotics only when prescribed.
- 2 - Strictly follow the prescription.
- 3 - Do not re-use an antibiotic without medical prescription, even if you want to treat a similar illness.
- 4 - Never give your antibiotic to another person; maybe it is not adapted to her/his illness.
- 5 - After completion of treatment, return all unused drugs to your chemist's shop to ensure they will be disposed of correctly

**The following information is intended for medical or healthcare professionals only**

Ciprofloxacin 2 mg/ml Solution for infusion 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 2 mg/ml Solution for infusion and 30 minutes for 200 mg Ciprofloxacin 2 mg/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.

Unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin infusion solutions: 3.5-4.6).

After intravenous initiation of treatment, the treatment can be continued orally as well.

## Module 4

### Labelling

*The labelling below is the label text agreed at the end of the decentralised procedure. The marketing authorisation holder has stated that it is not intending to market either product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL and labelling for review to the regulatory authority before marketing either product.*

|  |
|--|
| <b>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING OVERWRAPPING AND BAG</b> |
|--|

**1. NAME OF THE MEDICINAL PRODUCT**

Ciprofloxacin 2mg/ml Solution for infusion

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Contains 2mg ciprofloxacin per ml.

**3. LIST OF EXCIPIENTS**

Also contains: lactic acid, glucose monohydrate, hydrochloric acid for pH adjustment and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion.

400mg ciprofloxacin per 200ml bag

10 x200ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.

See leaflet for further information.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

(Not applicable)

**8. EXPIRY DATE**

EXP {MM/YYYY}

Read the package leaflet before use.

For use as directed by the physician.

For single use only.

**9. SPECIAL STORAGE CONDITIONS**

‘Store in the original container to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

(Not applicable)

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<to be completed nationally>

**12. MARKETING AUTHORISATION NUMBER(S)**

<to be completed nationally>

**13. BATCH NUMBER**

Lot {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

<to be completed nationally>

**15. INSTRUCTIONS ON USE**

(Not applicable)

**16. INFORMATION IN BRAILLE**

(Not applicable)

|  |
|--|
| <b>PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING OVERWRAPPING AND BAG</b> |
|--|

**1. NAME OF THE MEDICINAL PRODUCT**

Ciprofloxacin 2mg/ml Solution for infusion

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Contains 2mg ciprofloxacin per ml.

**3. LIST OF EXCIPIENTS**

Also contains: lactic acid, glucose monohydrate, hydrochloric acid for pH adjustment and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion.

200mg ciprofloxacin per 100ml bag

10 x100ml

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.

See leaflet for further information.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

(Not applicable)

**8. EXPIRY DATE**

EXP {MM/YYYY}

Read the package leaflet before use.

For use as directed by the physician.

For single use only.

**9. SPECIAL STORAGE CONDITIONS**

‘Store in the original container to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

(Not applicable)

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<to be completed nationally>

**12. MARKETING AUTHORISATION NUMBER(S)**

<to be completed nationally>

**13. BATCH NUMBER**

Lot {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

<to be completed nationally>

**15. INSTRUCTIONS ON USE**

(Not applicable)

**16. INFORMATION IN BRAILLE**

(Not applicable)

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING OVERWRAPPING AND BAG**

**1. NAME OF THE MEDICINAL PRODUCT**

Ciprofloxacin 2mg/ml Solution for infusion

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Contains 2mg ciprofloxacin per ml.

**3. LIST OF EXCIPIENTS**

Also contains: lactic acid, glucose monohydrate, hydrochloric acid for pH adjustment and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion.

400mg ciprofloxacin per 200ml bag

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.

See leaflet for further information.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

(Not applicable)

**8. EXPIRY DATE**

EXP {MM/YYYY}

Read the package leaflet before use.

For use as directed by the physician.

For single use only.

**9. SPECIAL STORAGE CONDITIONS**

‘Store in the original container to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

(Not applicable)

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<to be completed nationally>

**12. MARKETING AUTHORISATION NUMBER(S)**

<to be completed nationally>

**13. BATCH NUMBER**

Lot {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

<to be completed nationally>

**15. INSTRUCTIONS ON USE**

(Not applicable)

**16. INFORMATION IN BRAILLE**

(Not applicable)

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING OVERWRAPPING AND BAG****1. NAME OF THE MEDICINAL PRODUCT**

Ciprofloxacin 2mg/ml Solution for infusion

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

Contains 2mg ciprofloxacin per ml.

**3. LIST OF EXCIPIENTS**

Also contains: lactic acid, glucose monohydrate, hydrochloric acid for pH adjustment and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Solution for infusion.

200mg ciprofloxacin per 100ml bag

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

For intravenous use.

See leaflet for further information.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN**

Keep out of the reach and sight of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

(Not applicable)

**8. EXPIRY DATE**

EXP {MM/YYYY}

Read the package leaflet before use.

For use as directed by the physician.

For single use only.

**9. SPECIAL STORAGE CONDITIONS**

'Store in the original container to protect from light

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

(Not applicable)

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

<to be completed nationally>

**12. MARKETING AUTHORISATION NUMBER(S)**

<to be completed nationally>

**13. BATCH NUMBER**

Lot {number}

**14. GENERAL CLASSIFICATION FOR SUPPLY**

<to be completed nationally>

**15. INSTRUCTIONS ON USE**

(Not applicable)

**16. INFORMATION IN BRAILLE**

(Not applicable)

## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, Belgium Germany, Italy, the Netherlands, Spain and the UK considered that the application for Ciprofloxacin 2mg/ml Solution for Infusion could be approved. The product is a prescription only medicine (POM) used in adults to treat the following bacterial infections:

- 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)

Ciprofloxacin 2 mg/ml Solution for Infusion is used in children and adolescents to treat the following bacterial infections:

- Broncho-pulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- Complicated urinary tract infections and pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)
- Severe infections in children and adolescents when this is considered to be necessary.

This application for Ciprofloxacin 2 mg/ml Solution for Infusion is submitted as an abridged standard application according to Article 10.1 of Directive 2001/83/EC, claiming to be a generic medicinal product to Ciproxin Infusion 2mg/ml, first authorised in the United Kingdom to Bayer PLC in February 1987.

Ciprofloxacin is a synthetic fluorinated 4-quinolone derivative antibiotic, indicated for the treatment of a wide range of infections caused by susceptible organisms, including those caused by organisms resistant to aminoglycosides, penicillins and cephalosporins. It acts via the inhibition of bacterial DNA gyrase.

No new preclinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known active substance. No clinical studies have been performed and none are required for this application as the pharmacology of ciprofloxacin is well-established. No clinical pharmacology data is required for this generic infusion solution.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

**II. ABOUT THE PRODUCT**

|   |   |
|---|---|
| Name of the product in the Reference Member State | Ciprofloxacin 2mg/ml Solution for Infusion  |
| Name(s) of the active substance(s) (INN)          | Ciprofloxacin   |
| Pharmacotherapeutic classification (ATC code)     | Fluoroquinolones (J01MA02)  |
| Pharmaceutical form and strength(s)               | 2mg/ml Solution for Infusion  |
| Reference numbers for the Decentralised Procedure | UK/H/1443/001/DC  |
| Reference Member State                            | United Kingdom  |
| Member States concerned                           | Belgium, Germany, Italy, The Netherlands, Spain   |
| Marketing Authorisation Number(s)                 | PL 19364/0032   |
| Name and address of the authorisation holder      | UKR Regulatory Affairs Limited<br>First floor, Chiltern House, Thame Road<br>Haddenham, Buckinghamshire, HP17 8BY |



### III SCIENTIFIC OVERVIEW AND DISCUSSION

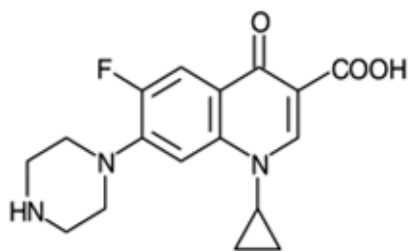
#### III.1 QUALITY ASPECTS

##### S. Active substance

INN/Ph.Eur name: Ciprofloxacin

Chemical name: Cyclopropyl-6-fluoro-4-oxo-7-(1-piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid -1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid.

Structural formula:



Molecular formula:  $C_{17}H_{18}FN_3O_3$

Appearance: white to pale yellow crystalline powder.  
Practically insoluble in water, very slightly soluble in diluted acetic acid and sparingly soluble in diluted ammonia.  
Ciprofloxacin melts at about 255°C, with decomposition.

Molecular weight: 331.35 g/mol

Ciprofloxacin is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture of the active substance ciprofloxacin from its starting materials are controlled by a Certificate of Suitability.

An appropriate retest period has been proposed based on stability data submitted for the active substance ciprofloxacin.

An appropriate specification is provided for the active substance, with suitable test methods and limits. The methods of testing and limits for residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specification.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised. Suitable certificates of analysis have been provided for all reference standards used.

Appropriate stability data have been generated showing the active substance to be a physically and chemically stable drug, and supporting an appropriate retest period.

##### P. Medicinal Product

###### Other Ingredients

Other ingredients are the pharmaceutical excipients glucose monohydrate, water for injections, hydrochloric acid and lactic acid.

All excipients comply with their European Pharmacopoeia monograph.

None of the excipients contain materials of animal or human origin. No genetically modified organisms (GMO) have been used in the preparation of this product.

### **Pharmaceutical Development**

The objective of the development programme was to produce a product that could be considered a generic medicinal product of Ciproxin Infusion 2mg/ml (Bayer PLC, February 1987).

The applicant has provided a suitable product development section. Justifications for the use and amounts of each excipient have been provided and are valid. Comparative impurity profiles have been provided for the finished product versus the reference product Ciproxin Infusion 2mg/ml (Bayer PLC).

### **Manufacturing Process**

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated with production scale batches and has shown satisfactory results.

### **Finished Product Specification**

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

### **Container-Closure System**

The product is packaged in bags composed of flexible plasticised PVC (polyvinylchloride), overpouched with a PET metal/PE black film.

Specifications and certificates of analysis for the packaging used have been provided. The product is packaged in 100ml and 200ml bags.

Satisfactory specifications and certificates of analysis have been provided for all packaging components. All primary packaging complies with the European Pharmacopoeia Type I and relevant regulations regarding use of materials in contact with food.

### **Stability of the product**

Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of three years for an unopened product with storage conditions "Store in original container to protect from light."

The shelf life also states that for an opened product, "The product is for single use only and once opened, the product should be used immediately after removal from the overpouch."

### **Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL), Labels**

The SPC, PIL and labelling are pharmaceutically acceptable.

User testing results have been submitted for a typical PIL for this product. The results indicate that the PIL is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA forms**

The MAA form is pharmaceutically satisfactory.

**Expert report**

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**

The grant of a marketing authorisation is recommended.

**III.2 PRE-CLINICAL ASPECTS**

The pharmacodynamics, pharmacokinetics and toxicological properties of ciprofloxacin are well-known. As ciprofloxacin is a widely used, well-known active substance, the applicant has not provided any additional studies and none are required.

The pre-clinical expert report is based on literature sources and has been written by an appropriately qualified person.

### III.3 CLINICAL ASPECTS

#### 1. Introduction

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

**The clinical overview has been written by an appropriately qualified physician. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.**

#### 2. Clinical study reports

No bioequivalence studies have been performed and none are required for this application, as the applicant's product is similar to the reference product in terms of qualitative and quantitative composition and is expected to perform identically *in vivo*. A human bioavailability study is not relevant to this application as the compound is intended for intravenous infusion.

#### 3. Post marketing experience

Ciprofloxacin has a well-recognised efficacy and an acceptable level of safety in the indications approved for Ciproxin Infusion 2mg/ml, and corresponding products have been widely used in many countries. Therefore, the submission of PSUR at the renewal of the marketing authorisation is supported.

#### 4. Benefit-Risk assessment

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with ciprofloxacin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

#### 5. Conclusions

The grant of a marketing authorisation for Ciprofloxacin 2mg/ml Solution for Infusion is recommended from a clinical viewpoint.

#### **IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY**

The important quality characteristics of Ciprofloxacin 2mg/ml Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

#### **PRECLINICAL**

No new preclinical data were submitted and none are required for an application of this type.

#### **CLINICAL**

No bioequivalence studies have been performed and none are required for this application, given the composition of the product and its intended route of administration.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

#### **RISK-BENEFIT ASSESSMENT**

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with ciprofloxacin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

## Module 5

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

| Date submitted | Application type | Scope | Outcome |
|----------------|------------------|-------|---------|
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |
|                |                  |       |         |