CIPROFLOXACIN SOLUTION FOR INFUSION 2 MG PER ML

PL 24598/0009

UKPAR

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LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Noridem Enterprises Limited a Marketing Authorisation (licence) for the medicinal product Ciprofloxacin Solution for Infusion 2 mg per ml (Product Licence number 24598/0009). This medicine is available by prescription only.

Ciprofloxacin is an antibiotic that is used to treat a number of bacterial infections. It stops bacteria from multiplying by interfering with DNA replication in the bacterial cell.

Ciprofloxacin Solution for Infusion 2 mg per ml raised no clinically significant safety concerns and it was therefore judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

CIPROFLOXACIN SOLUTION FOR INFUSION 2 MG PER ML

PL 24598/0009

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted a marketing authorisation for the medicinal product Ciprofloxacin Solution for Infusion 2 mg per ml (PL 24598/0009) to Noridem Enterprises Limited on 3 October 2006. This product is a prescription only medicine.

This is a national application submitted under Article 10.1 of Directive 2001/83, claiming essential similarity to Ciproxin Infusion 2mg/mL (PL 00010/0150) authorised in the UK to Bayer PLC on 3 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.

PHARMACEUTICAL ASSESSMENT REPORT

1 REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

This is not required. The product is manufactured by DEMO SA, 21st km National Road Athens – Lamia, 14568 Kryoneri, Athens, Greece. A copy of the drug product manufacturer's licence (Ref 20888; dated June 2006) as issued by the Hellenic Republic National Organization for Medicines has been provided. This covers the preparation of sterile products by the site. A copy of DEMO SA's GMP certificate has been supplied.

2 INTRODUCTION

This is a National Abridged Application for 2mg/mL ciprofloxacin solution for infusion. The application is submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application claiming essential similarity to the brand leader, Ciproxin Infusion 2mg/mL (PL 00010/0150). The marketing authorisation for the brand leader was granted to Bayer PLC in the UK on 3 February 1987, therefore the ten year rule is met. The active substance is used in the basic form as ciprofloxacin lactate, which is the same as the brand leader. The product will be available on prescription only (POM).

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.

The applicant has indicated a desire for mutual recognition following grant of the marketing authorisation, although the concerned member states have not been specified at this stage.

3 DRUG SUBSTANCE

3.1 GENERAL INFORMATION

The active substance is the subject of a DMF (UK reference number 08512-A6398) that has previously been assessed and accepted for use in products for the UK market.

A letter from the DMF holder, authorising access to the DMF in relation to the assessment of this application, has been provided.

3.2 CONTROL OF DRUG SUBSTANCE

A copy of the specification used by the finished product manufacturer (Demo SA) is provided, together with certificates of analysis for two batches of active substance. The proposed specification is similar to that of the drug substance manufacturer and complies with the current edition of the Ph. Eur. Full details are provided of the analytical procedures used. These are in line with the Ph. Eur and are acceptable. In-house tests in line with the Ph. Eur are performed by the active substance manufacturer for microbial limits and endotoxins. A signed declaration has been provided from the drug substance manufacturer confirming that no ingredients of animal / human origin or susceptible to TSE have been used in the manufacture of the active substance.

The finished product manufacturer confirms the quality of the drug substance on each receipt by analytical testing according to the requirements of the Ph Eur. The finished product manufacturer routinely performs all tests included in the 'Analytical Procedures' section of the dossier on receipt of the active substance and issues a Certificate of Analysis accordingly to allow the active ingredient to be released and used in production. It is noted that tests for microbial limits and endotoxins are not performed by the finished product manufacturer on receipt. These results are

accepted from the suppliers' Certificate of Analysis; this is in accordance with GMP requirements as the drug product is subsequently terminally sterilized. Certificates of Analysis are provided.

The particle size of the active substance has been determined in three different batches using six sieves of varying size. All three batches presented with a similar particle size distribution and this demonstrates that there is consistency between batches. Suitable limits for particle size are included in the drug substance specification of the finished product manufacturer.

3.3 REFERENCE STANDARDS OR MATERIALS

The primary reference standard is the current Lot of European Pharmacopoeial Chemical Reference Standard (EPCRS) ciprofloxacin hydrochloride. Working standards are standardised against this as per the Standard Operating Procedure.

The current Lots of EPCRS ciprofloxacin impurity A CRS and ciprofloxacin hydrochloride for peak identification EPCRS are also used.

3.4 STABILITY

Reference is made to the DMF. The re-test period adopted for the drug substance by the finished product manufacturer is 12 months from date of receipt of the active ingredient. The retest period established by the drug substance manufacturer is four years.

4 DRUG PRODUCT

4.1 DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT

The clear, yellowish, sterile and non-pyrogenic aqueous solution contains 2mg/mL of ciprofloxacin as ciprofloxacin lactate (2.54mg). The product is packed in 100mL and 200mL polypropylene plastic bags with rubber (type 1) closures and aluminium caps with plastic flip-top covers.

The bags are enclosed in transparent plastic pouches and packed into boxes of 10 bags (100mL) and 5 bags (200mL). The qualitative composition of the product is outlined as follows:

Composition of Ciprofloxacin Solution for Infusion 2mg / mL

Ingredient	Function	Reference to Standard
Active Substance		
Ciprofloxacin as Ciprofloxacin lactate[1]	Active	Ph. Eur
Excipients		
Lactic acid	Solubilising agent	Ph. Eur
Sodium chloride	Electrolyte, makes the solution isotonic	Ph. Eur
Hydrochloric acid	pH adjuster	Ph. Eur
Water for injections	Vehicle	Ph. Eur

1 Ciprofloxacin lactate is formed by the interaction between ciprofloxacin and lactic acid

4.2 PHARMACEUTICAL DEVELOPMENT

The aim of the pharmaceutical development was to develop a sterile solution for infusion containing the antibacterial, ciprofloxacin, that was essentially similar to the innovator product, Ciproxin. The qualitative composition of the applicant's product is the same as that of the brand leader. The product to which this marketing authorisation application refers is currently covered by a monograph in the BP 2005.

4.2.1 Components of the Drug product

Drug substance
As the active substance, ciprofloxacin is practically insoluble in water, it is not possible for it to be administered intravenously as an aqueous solution. This is overcome by using lactic acid, which interacts with ciprofloxacin to form ciprofloxacin lactate that is soluble in water.

Excipients
Lactic acid was used to interact with ciprofloxacin to form water soluble ciprofloxacin lactate. The amount of lactic acid used is within the specified USP limits of 0.576 to 0.704mg.

In line with the BP, isotonicity of the solution is achieved with the use of sodium chloride and water for injections used as the solvent. The pH of the solution is adjusted with hydrochloric acid as per the BP monograph.

Compatibility of the excipients in the formulation and with the drug substance is evident from the stability studies (section 4.8).

4.2.2 Drug Product

Formulation development
The product was developed according to the corresponding BP monograph. No further details are provided.

Physicochemical and biological properties
The pH range of the product is in line with the BP. The solution is sterile and has a suitable endotoxin limit concentration.

Manufacturing process development
The solution is prepared in a Grade C clean room. The critical processing area of the machine where filling of the bags takes place is a Grade A clean zone. All areas comply with current EUR GMP guidelines.

Briefly, the manufacturing process incorporates various aseptic sterilisation steps. The bulk of the solution is pre-filtered. During the filling process, the bulk solution is filtered again, with the bulk solution being filtered through a third sterilised filter immediately prior to the filling point. The integrity of all 0.2µm filters is verified before and immediately after use.

The rubber closures and aluminium caps are subjected to steam sterilisation (at 121°C/30 minutes) before use. Filling of solution takes place in a nitrogen atmosphere in order to avoid any oxidation of the drug substance. The nitrogen gas used is filtered using filters that comply with specifications and are tested routinely before and after use. To minimise any bioburden prior to terminal sterilisation, a maximum period of 16 hours has been set between filling of the bags and autoclaving.

Container closure system
The finished product is packed in polypropylene plastic bags that comply with the Ph. Eur requirements for plastic containers for aqueous parenteral preparations. The bags are closed with type I rubber closures and sealed with aluminium caps with a flip-top cover. The bags are then enclosed in a transparent plastic pouch. Further details on the container closure system are given in section 4.7. These are then packed into carton boxes in order to protect the product from light.

Data are provided of an initial test performed to determine the permeability of the plastic pouch. No significant variation in the weight of the product was observed after 6 months at 40 ± 2°C (R.H. 25 ± 5%). According to the results, the immediate packaging of the product wrapped with the plastic pouch can be considered impermeable.

Microbial attributes
Samples of filled bags are collected throughout the filling process and tested for the detection of any leaks using a dye intrusion leak test.

Compatibility
See section 4.8.1.

4.3 MANUFACTURE

4.3.1 Manufacturer

The product is manufactured by DEMO SA at 21st km National Road Athens – Lamia, 14568 Kryoneri, Athens, Greece. A copy of the manufacturer's licence (Ref 20888; dated June 2006) as issued by the Hellenic Republic National Organization for Medicines has been provided. This covers the preparation of sterile products by the site.

4.3.2 Batch Formula

Batch formulas are provided and supported by batch data.

4.3.3 Description of Manufacturing Process and Process Controls

A flow diagram summarising the manufacturing process and in-process controls has been provided. Briefly, the method involves the following:

- *Step 1: Cleaning and sterilization of manufacturing equipment.*

All parts of the manufacturing equipment in contact with the product are cleaned with purified water and water for injections and then sterilised with clean steam before use. Rubber closures and aluminium caps are subjected to steam sterilisation at 121°C for 30 min.

- *Step 2: Preparation of solution A.*

The ciprofloxacin and lactic acid are dissolved in water for injection into a stainless steel vessel. The pH of the solution is adjusted using a 10% w/v hydrochloric acid solution

- *Step 3: Preparation of solution B.*

The required quantity of sodium chloride is dissolved in water for injection into the premixer.

- *Step 4: Preparation of final bulk solution - Sterile filtration*

Solution A is transferred into the premixer and mixed with solution B. The bulk solution is filtered and immediately transferred into a sealed stainless steel hold tank. The solution is diluted to the final volume with water for injections.

- *Step 5: Filling*

The solution is transferred under N_2 pressure to the filling machine and filtered. The solution is filtered close to the filling point of the machine and filled into the polypropylene bags under N_2 pressure.

- *Step 6: Terminal Sterilization*

The filled bags are terminally sterilized in the autoclave at 121°C for 20 minutes in line with Ph. Eur conditions. All steps of autoclaving are recorded.

- *Step 7: Packaging*

The sterilised bags are labelled, overpacked in plastic pouches and packaged in carton boxes.

4.3.4 Control of Critical Steps and Intermediates

There are no intermediates in this product. A number of in-process controls are performed at various stages of the manufacturing process.

- *Preparation of solutions A & B*:

Stirring time, stirring speed and pH are monitored

- *Filtration processes*:

The integrity of the sterilising filters is verified before and after filtration of the solution following a forward flow test.

- *Final bulk solution*:

Stirring time and stirring speed are monitored. The bulk solution is also sampled before filling and tested for:

- Description
- Content of Ciprofloxacin
- Content of Sodium Chloride
- pH
- Bioburden
- Bacterial endotoxin

- *Filling*:

During filling, the bags are sampled and tested for:

- Filling volume (on a sampling plan)
- Leak detection
- Visual Inspection
- Bioburden (on samples of filled bags taken before terminal sterilisation)

- *Terminal sterilisation*:

It is verified that the required conditions of time and temperature (121°C for 20min) have been achieved.

4.3.5 Process Validation and/or Evaluation

Validation was performed on three production scale batches of both the 100ml [30775-04007, 30775-04008, 30775-04009] and 200ml [30776-04005, 30776-04006, 30776-04007] bags.

Tests are performed for:

> Characteristics (clarity, colour & odour of solution)
> Identification of active ingredient
> Content of ciprofloxacin
> Content of sodium chloride
> Related substances
> pH
> Bioburden
> Particulate matter
> Bacterial endotoxins
> Sterility
> Extractable volume
> Visual inspection
> Leak detection test

Summary results of the validation studies are provided. These show that samples were analysed for various physicochemical characteristics, as well as bacterial endotoxins and bioburden, after preparation of the solution in the premixing tank, during stirring of the solution in the main holding tank prior to filtration (samples from the beginning, middle and end), after sterile filtration of the solution and during filling of the solution into polypropylene bags (samples from the beginning, middle and end). All results showed the bioburden and endotoxin levels to be below the maximum

allowable limit. Terminal sterilisation of the product showed bioburden and endotoxin levels to be acceptable.

Full details of sterility testing and validation data are provided and demonstrate that the method complies with the Ph. Eur 2.6.1. Details of the composition of the filters, release of extractables and adsorption characteristics have been provided and are satisfactory.

Ciprofloxacin solution in 100ml and 200ml polypropylene bags is terminally sterilized in an autoclave at 121° for 20 minutes. These conditions ensure that all items of the load are exposed uniformly to the sterilization conditions in accordance with the European Pharmacopoeia. The data show the distribution of thermocouples and bioindicators and that the F_0 value during sterilisation is > 15mins. Data are provided for the equilibration time during the validation cycle (the time from when the vessel chamber achieves sterilisation conditions to the time when the product achieves the same temperature as the vessel). The maximum equilibration time is 3 minutes. The details are acceptable.

Full details of the validation studies of the bacterial endotoxin test are provided and the results obtained for the validation studies demonstrate that the method is validated in line with the Ph. Eur 2.6.14. Absence of interfering factors in the product has also been demonstrated.

4.4 CONTROL OF EXCIPIENTS

No novel excipients are used in this product.

All excipients comply with the current edition of the Ph. Eur. It is stated in the Quality Overall Summary that all excipients are tested upon receipt and that the water for injections is produced and tested according to the requirements of the Ph. Eur at Demo's facilities. It has been stated by the applicant that no excipients of animal or human origin are used and a declaration from the supplier of lactic acid has provided a satisfactory declaration regarding TSE status.

Certificates of analysis from the finished product manufacturer have been provided for all excipients. It is noted that lactic acid, sodium chloride and water for injections are tested for bacterial endotoxins.

The drug product manufacturer confirms that each batch of sodium chloride, in addition to lactic acid, is fully tested upon receipt in accordance with the relevant monographs of the current edition of the European Pharmacopoeia. Details have been provided in the Certificates of Analysis.

According to the corresponding monographs for lactic acid and sodium chloride in the current edition of the European Pharmacopoeia, there is no requirement for microbial contamination testing. However, there is a requirement for the control of bacterial endotoxins. The tests for bacterial endotoxins that are performed by the drug product manufacturer and the manufacturers of the excipients are shown in the Certificates of Analyses provided.

Purified Water (PW) and Water for Injections (WFI) are produced and tested at the drug product manufacturer's facilities in accordance with the requirements of the Ph. Eur. The specifications of the Purified Water and Water for Injections adopted by the manufacturer and representative Certificates of Analysis of three successive typical daily controls of PW and WFI are provided and are satisfactory.

4.5 CONTROL OF DRUG PRODUCT

4.5.1 Specification

The finished product specifications for the drug product at release and end of shelf life have been provided and all specifications and limits are satisfactory.

4.5.2 Analytical Procedures

Full details of all the analytical methods have been provided. Identification is performed using TLC and isocratic HPLC with a cation exchange resin column with UV. Content of ciprofloxacin and related substances is measured using reverse phase HPLC with UV detection.

4.5.2 Validation of Analytical Procedures

The HPLC method for content of ciprofloxacin is suitably validated with respect to accuracy, precision (intermediate precision and repeatability), linearity, specificity, stability of solution, robustness and ruggedness and system suitability.

The HPLC method for related substances is suitably validated with respect to accuracy, precision (intermediate precision and repeatability), linearity, specificity, stability of solution, robustness and ruggedness, system suitability, limit of detection and limit of quantitation.

The test for content of sodium chloride was validated with respect to accuracy, precision, linearity and ruggedness. The Ph. Eur tests for bacterial endotoxins, as well as for sterility, have been validated for this product.

4.5.3 Batch Analyses

Batch data are provided for three production scale batches of 100ml bags [30775-04007, 30775-04008, 30775-04009] and 200ml bags [30776-04005, 30776-04006, 30776-04007] which were manufactured between May and July 2004. Details of the batch number of active substance used to make the batch analysis batches have been provided.

Certificates of analysis are provided for all batches showing that all required specification limits were met. This is acceptable.

4.5.4 Characterisation of impurities

No further characterisation data, beyond that performed by the active substance manufacturer, has been presented. The proposed finished product specification impurity limits are considered adequate.

4.5.5 Justification of Specifications

This specification is consistent with what has been approved previously and is, therefore, justified.

4.6 REFERENCE STANDARDS OR MATERIALS

As per section 3.3, the primary reference standard is the current Lot of EPCRS ciprofloxacin hydrochloride. Working standards are standardised against this as per the Standard Operating Procedure.

The current Lots of EPCRS Ciprofloxacin Impurity A CRS and Ciprofloxacin hydrochloride for peak identification EPCRS are also used.

4.7 CONTAINER CLOSURE SYSTEM

The finished product is packed in 100mL and 200mL polypropylene plastic bags with rubber (type 1) closures and aluminium caps with plastic flip-top covers. The container design consists of a

container body, a large port suitable for the attachment of an infusion set, a small port that allows an injection to be made at the time of use and a hanger that allows the container to be suspended.

The container body and ports are made from the same material, which meets the Ph. Eur requirements for plastic containers for aqueous parenteral preparations. The container is sufficiently transparent to allow examination of the contents. The small port is closed with a type I rubber closure and sealed with a flip-off aluminium cap. The large port is closed with a plastic snap-on cap, to ensure a high level of hygiene during transport and storage. The snap-on cap is a protection cap used during storage and transport of the empty container, it is removed before filling and it does not come in contact with the solution inside the container.

The sealed bags are enclosed in a transparent high barrier plastic pouch, to minimise water loss and maintain the nitrogen atmosphere inside the bags. Finally, the wrapped bags are placed into carton boxes which provide protection of the solution from light.

Dimensional schematics, details of all manufacturers, specifications and analytical procedures used for control of the plastic containers, rubber closures, aluminium caps and plastic pouches are provided. For all packaging components batch analysis results are provided for three batches.

The proposed container closure system has been used for other marketed medicinal products. A list of these products has been provided. A list is also provided by the plastic bag supplier demonstrating that their container closure system is supplied for other medicinal products.

Written confirmation from the supplier of the plastic bags demonstrating compliance with Directive 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs, is provided.

The aluminium caps which are not in direct contact with the drug product are exempt from compliance with Directive 2002/72/EC. The stoppers are made of rubber and are also exempt from compliance with Directive 2002/72/EC. Confirmation from the suppliers of the aluminium caps and rubber stoppers that they comply with ISO 8362-6 and ISO 8871/ISO8362-2 are provided.

Potential leaching of plastic additives from the container into the product, sorption of the active ingredient in addition to leaching of label adhesives through the container to the solution have been studied. Data are provided for three batches manufactured in 2004. These were stored at 25 ± 2°C (R.H. 60 ± 5%) for 24 months and at 40 ± 2°C (R.H. 75 ± 5%) for 6 months. The bags were placed in the chambers in a horizontal position in order to keep the solution in contact with the rubber closures during the stability study. These three batches were analysed at the end of the stability study under both accelerated and long term conditions for levels of two additives (known to be present in the polypropylene bags) and the extraction profile. Results from the study showed migration of the leachables from the container/closure system into the pharmaceutical solution proved to be in the lowest possible limits through the end of the product's shelf life and after six months at 40 ± 2°C (R.H. 75 ± 5%). No migration was observed from the label adhesive. The compatibility of the packaging material and the drug product can be considered acceptable.

4.8 STABILITY

4.8.1 Stability Summary and Conclusion

Data are provided for the same production scale batches mentioned in section 4.5.3, tested under ICH conditions of real time (25 ± 2°C [R.H. 60 ± 5%]) and accelerated (40 ± 2°C [R.H. 75 ± 5%]) for 6 months. In addition, photostability and compatibility studies were performed.

- *Real time (25 ± 2°C [R.H. 60 ± 5%])*

Twenty four months real time data are provided. All batches met the required specification limits and support the proposed shelf life of 24 months for the unopened finished product.

- *Accelerated (40 ± 2°C [R.H. 75 ± 5%])*

Data for 6 months showed all batches to meet the proposed specification limits. The variation of the weight of the drug product was studied for six months at 40 ± 2°C (R.H. 25 ± 5%) in order to check the permeability of the polypropylene bag wrapped with a plastic pouch. Since no significant variation was observed (loss of weight <0.02%), the plastic bag wrapped with the plastic pouch can be considered impermeable. These studies were performed under ICH conditions and the data provided for loss of weight studies is acceptable.

- *Photostability*

These studies were performed on two batches, one close to the shelf life and the other close to the manufacturing date. Samples were exposed for a total of 1.2 million lux hours and tested for appearance, colour, pH, and content of ciprofloxacin and NaCl and related substances. They were stored under the following conditions in a photostability chamber maintained at 25 ± 2°C, in line with ICH Q1B option 1:

- samples not exposed to light
- samples in immediate container (PP bag) exposed to light
- samples in immediate container and in plastic pouch exposed to light
- samples in commercial packaging (in plastic pouch & carton box) exposed to light

Samples failed if unacceptable changes were observed, that is > 5% change in assay or failure to meet the specification limits. Results are provided for the end of the exposure period. The data showed that samples exposed to light in commercial packaging were similar to those of unexposed samples, thereby indicating that the carton protects the product from photodegradation. Samples exposed to light displayed out of specification results for assay (decrease) and impurities (increase).

The finished product is packed in a box containing multiple bags, that is boxes of 10 bags (100mL) and 5 bags (200mL). Section 6.4 of the SPC contains the following statement, 'if the product is advertently removed from the outer carton, the stability of the product is maintained for a period of up to three days in daylight'. Data supporting this statement has been provided for three batches of sample (manufactured 2004; tested 2005) exposed to ten days of daylight and tested daily for appearance, colour, pH, content of NaCl and ciprofloxacin and related substances; every two days for particulate contamination; and at the start and end of the study for sterility and bacterial endotoxins. The data showed all specification limits to be met and that the drug product is stable for the proposed time (three days) in daylight.

Compatibility

Data have been provided from a study to show the compatibility of the product with Ringer's IV solution, Ringer's lactate IV solution, sodium chloride 0.9%, fructose 10%, dextrose 5% and 10%, sodium chloride 0.45% plus dextrose 5% and sodium chloride 0.225% plus dextrose 5%. Samples used to perform the study were close to their expiry date. One 100-ml bag of ciprofloxacin solution for infusion and one 500-ml bottle of IV solution were used for each compatibility study (1:5). For the compatibility with Ringer lactate, dextrose 10% and fructose 10% solutions 1000-ml bottles of the IV solutions were used (1:10).

The contents of the 100-ml bag and of the 500-ml or 1000-ml bottle are transferred under laminar flow in a sterile bottle. The volumes of Ciprofloxacin solution and of the resulting solution were measured. The resulting preparations were stored at 25°C and at 4°C and examined for a total of 48 hours (1, 2, 4, 6, etc. hours after mixing) physically by visual inspection, chemically by HPLC analysis and microbiologically. Recovery below 95% of the initial concentration of ciprofloxacin was defined as significant loss.

In cases of recovery below 95% the control was stopped. Visible precipitates or pH changes greater than 1 unit indicated incompatibility. Parameters tested were appearance, pH, content of ciprofloxacin (mg/100mL), impurities, sterility and bacterial endotoxins. Based on the data provided, it has been stated by the applicant that the product is stable for 48 hours in all the tested solutions except with Ringer's solution, where it is stable for 12 hours.

4.9 BIOEQUIVALENCE / BIOAVAILABILITY

No bioequivalence study has been performed for this application, nor is it considered to be necessary. As the product is a solution for injection and bioavailability of the active from the product is considered to be immediate, bioequivalence is assumed. Please refer to the Medical Assessment Report.

4.10 ESSENTIAL SIMILARITY

The data provided show comparable results between the reference product and the test product. The reference product is qualitatively the same as the UK marketed brand leader product.

5 ASSESSOR'S COMMENTS ON MODULE I

5.1 SPC

This is satisfactory.

5.2 PATIENT INFORMATION LEAFLET

This is satisfactory.

5.3 LABEL

Colour mock-ups have been provided and are satisfactory.

5.4 APPLICATION FORM

The MAA form submitted is satisfactory.

6 ASSESSOR'S COMMENTS ON THE QUALITY OVERALL SUMMARY

The Quality Overall Summary has been written by a suitably qualified chemist. It is an adequate précis of the dossier.

7 ASSESSOR'S OVERALL CONCLUSIONS

Granting of a Marketing Authorisation is recommended.

PRECLINICAL ASSESSMENT REPORT

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT REPORT

1 INTRODUCTION

1.1 TYPE OF APPLICATION AND REGULATORY BACKGROUND

This is a national application made under Article 10.1 for Ciprofloxacin Solution for infusion 2mg per ml. The original and reference medicinal product is Ciproxin for infusion (PL 00010/0150), granted in 1987 to Bayer plc.

There are no other MA pending, approved or refused, inside or outside the EEA for the same product. The applicant is considering a subsequent MRP.

1.2 CLINICAL BACKGROUND

Ciprofloxacin is a synthetic 4-quinolone derivative anti-bacterial agent of the fluoroquinolone class. As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Ciprofloxacin is particularly active against gram-negative bacteria, including *salmonella* spp*, shigella* spp*, campylobacter* spp*, neisseria* spp, and *pseudomonas* spp; but has only moderate activity against gram-positive bacteria such as *streptococcus pneumoniae* and *enterococcus feacalis*. In fact, ciprofloxacin is not the first choice for pneumococcal pneumonia. It has also activity against *Chlamydia* and some *mycobacteria*. Most anaerobic organisms however are not susceptible.

1.3 INDICATIONS

Ciprofloxacin is indicated in the treatment of infections by susceptible organisms, most notably pneumonia, urinary tract infections, prostatitis, bacterial enteritis, skin and soft tissue infections caused by gam-negative bacteria, osteomyelitis, intra-abdominal infections, infections in immuno-suppressed patients and acute exacerbation of cystic fibrosis in children and adolescents.

1.4 DOSE AND DOSE REGIMEN

These are determined by the type and severity of the infection, and age, weight and renal function of the patient. No adjustment is necessary in hepatic impairment.

1.5 GCP ASPECTS

No clinical trials were needed for this type of application, hence no GCP certification is required.

1.6 ORPHAN MEDICINAL PRODUCTS

Not applicable.

1.7 PAEDIATRIC DEVELOPMENT PROGRAMME

Ciprofloxacin is contraindicated in children under 5.

1.8 SCIENTIFIC ADVICE

Not applicable

1.9 LEGAL STATUS

POM

2 CLINICAL PHARMACOLOGY

2.1 PHARMACOKINETICS

The AUC increases dose proportionately after administration of both single and repeated oral (tablet) and intravenous doses. The pharmacokinetic profile of intravenous ciprofloxacin was shown to be linear over the dose range (100mg – 400mg). Ciprofloxacin is widely distributed and has a high volume of distribution in the tissues, although this is slightly less in the elderly. Protein binding is low (between 19 – 40%).

Only 10 – 20% of a single oral or intravenous dose is eliminated as metabolites (which exhibit lower activity than the parent drug), the remainder being eliminated mainly by the kidney and to a lesser extent in the faeces. Renal elimination takes place mainly during the first 12 hours after dosing and renal clearance levels suggest that active secretion by the renal tubules occurs in addition to normal glomerular filtration. The elimination kinetics are linear and, after repeated dosing at 12 hourly intervals, no further accumulation is detected after the distribution equilibrium is attained (at 4 – 5 half lives). The elimination half-life of unchanged ciprofloxacin over a period of 24 – 48 hours post-dose is 3.1 – 5.1 hours.

2.2 BIOEQUIVALENCE

Since this is an aqueous intravenous formulation no BE trial is required

2.3 PHARMACODYNAMICS

Effectively, the pharmacodynamics of ciprofloxacin relate to its antibacterial activity. As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

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

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

3 CLINICAL EFFICACY

The applicant presents a comprehensive review of published data with regards to clinical efficacy of ciprofloxacin in the proposed indications.

3.1 ASSESSORS' OVERALL CONCLUSIONS ON CLINICAL EFFICACY

This is acceptable for this type of application. There would be no particular concerns for a generic formulation of ciprofloxacin for intravenous use.

4 CLINICAL SAFETY

The clinical overview summarises data from published literature and post marketing experience of all types of formulations (oral and parenteral) of ciprofloxacin.

4.1 ASSESSOR'S OVERALL CONCLUSIONS ON CLINICAL SAFETY

The safety profile of ciprofloxacin has been well established in the past. There would be no particular concerns for a generic formulation provided that the safety aspects are well covered in the relevant sections of the SPC.

5 EXPERT REPORTS

The clinical expert is Dr. Peter JH Tooley, a qualified physician acting as a pharmaceutical consultant.

6 PRODUCT LITERATURE

6.1 SPC

The proposed SPC is based on that of the reference product but has been updated to comply with the latest guidance (QRD template and NfG on antimicrobials [CPMP/EWP/558/95 rev 1]) and to incorporate the latest safety updates.

6.2 PATIENT INFORMATION LEAFLET

The PIL is satisfactory

6.3 LABEL

No medical comments

6.4 APPLICATION FORM

No medical comments

7 OVERALL CONCLUSION

7.1 RECOMMENDED CONDITIONS FOR MARKETING AUTHORISATION

A MA can be granted

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ciprofloxacin Solution for Infusion 2 mg per ml (Product Licence number 24598/0009) are well defined and controlled. The specification and batch analysis results confirm consistancey 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.

EFFICACY AND SAFETY

The efficacy of ciprofloxacin has been well documented in the past. No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk benefit ratio is considered to be positive.

CIPROFLOXACIN SOLUTION FOR INFUSION 2 MG PER ML

PL 24598/0009

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 24 November 2005
2	Following initial assessment of the application the MHRA requested further information relating to the clinical dossier on 16 May 2006 and the quality dossier on 17 May 2006
3	The applicant responded to the MHRA's request, providing further information on the clinical dossier on 2 August 2006 and the quality dossier on 17 August 2006
4	Following assessment of the response the MHRA requested further information relating to the quality dossier on 24 August 2006
5	The applicant responded to the MHRA's request, providing further information on the quality dossier on 30 August 2006
6	Following assessment of the response the MHRA requested further information relating to the quality dossier on 12 September 2006
7	The applicant responded to the MHRA's request, providing further information on 2 October 2006
8	The application was determined on 3 October 2006

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2 mg/ml Solution for Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 ml polypropylene bag:
Each polypropylene bag contains 254.4 mg ciprofloxacin lactate equivalent to 200 mg ciprofloxacin.

200 ml polypropylene bag:
Each polypropylene bag contains 508.8 mg ciprofloxacin lactate equivalent to 400 mg ciprofloxacin.

For full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Clear, yellowish, sterile and non-pyrogenic aqueous solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults: Treatment of the following infections when caused by ciprofloxacin-sensitive pathogens:

Infections of
- the respiratory tract. Ciprofloxacin may be indicated for treating pneumonia due to gram-negative pathogens. Ciprofloxacin is not the drug of choice for the treatment of pneumococcal pneumonia

- the ear and the sinuses, especially when gram-negative bacteria are implicated

- the urinary tract, such as complicated infections and pyelonephritis

- the genital organs, including gonorrhoea and prostatitis

- the pelvic organs, such as salpingitis, endometritis and pelvic inflammatory disease

- intra-abdominal organs, including peritonitis and biliary tract infections

- enteric (typhoid) fever

- the skin and soft tissue

- the bones and joints

- severe systemic infections: septicaemia, infections in immunosuppressed patients

Children and adolescents:

Acute pulmonary exacerbation of cystic fibrosis in children and adolescents (5-17 years) caused by *Pseudomonas aeruginosa*.

Ciprofloxacin is not recommended for other indications in this age group.

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

4.2 Posology and Method of Administration

Posology
The dose of intravenous ciprofloxacin is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, weight and renal function of the patient.

The following dose recommendations are provided as a guideline and refer to intravenous dosing only (Note that different dose recommendations apply to oral administration of ciprofloxacin)

Adults
The dosage range for adults is 100 - 400 mg twice daily.

The following dosages are recommended for specific types of infections:
Table 1: Recommended Adult Dosage

Indication	Treatment
	Dosage iv (mg ciprofloxacin)
Gonorrhoea (uncomplicated infections)	100mg single dose
Urinary tract infections	100mg twice daily
Adult patients with cystic fibrosis and lung infections	400mg twice daily
Other infections in adults	200-400mg twice daily

Elderly
Although higher ciprofloxacin serum levels are achieved in elderly patients, no adjustments of dosage is necessary.

Children and adolescents (5-17years)
10 mg/kg intravenously three times daily (maximum daily dose 1200mg). The infusion should be administered over 60 minutes. Dosing in children with impaired renal and/or hepatic function has not been studied.

Impaired Renal Function
Except in patients with severe renal impairment (serum creatinine >265micromole/l or creatinine clearance <20ml/minute), dosage adjustments are not usually required. If adjustment is necessary, this may be achieved by reducing the total daily dose by half,

although monitoring of drug serum levels provides the most reliable basis for dose adjustment.

Impaired Hepatic Function
No adjustment of dosage is necessary
Duration
The duration of treatment depends upon the severity of the disorder and on the clinical and bacteriological course. Treatment that has been initiated with intravenous injection may be switched to oral therapy according to the condition of the patient.
Acute infections: the usual total treatment period is 5 - 7 days.

Acute and chronic infections (e.g. osteomyelitis and prostatitis, etc): generally, where the causative organism is known to be sensitive to ciprofloxacin, these infections should be treated for at least three days after the signs and symptoms of the infection have disappeared.

Acute pulmonary exacerbation of cystic fibrosis associated with P. aeruginosa infection in paediatric patients (aged 5 - 17 years): The usual treatment period is 10 - 14 days.

Method of Administration
The product should be infused directly and administered over 30-60 minutes. The 200ml (400mg) dose should be infused over 60 minutes.
Intravenous therapy may be followed by oral administration of ciprofloxacin where necessary and where appropriate. However, the dose recommendations for tablets are not the same as for the intravenous infusion.

4.3 Contraindications

Ciprofloxacin is contra-indicated in

- patients with a previous history of hypersensitivity to ciprofloxacin or to other (fluoro)quinolones or to any of the other ingredients
- patients with a history of tendon disorders related to fluoroquinolone administration
- pregnancy and breastfeeding
- children and growing adolescents except for the treatment of acute pulmonary exacerbation of cystic fibrosis in children aged 5-17 years.
- Children under 5 years.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine-induced side-effects (hypotension, somnolence) can occur.

4.4 Special warnings and precautions for use

In the event of hypersensitivity, which in some instances can occur after the first administration, therapy should be discontinued.

In patients with epilepsy or other lesions of the central nervous system (eg reduced convulsion threshold, a history of seizures, diminished cerebral blood flow, changes in brain structure or stroke) ciprofloxacin is only to be used after carefully weighing the benefits against the risk, because the possibility of central nervous side effects puts these patients at increased risk.

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

Pseudomembranous colitis is a particular form of enterocolitis that can occur with antibiotics (in most cases due to *Clostridium difficile*). If severe and persistent diarrhoea occurs during or after treatment, the doctor should be consulted. Even if *Clostridium difficile* is only suspected, administration of ciprofloxacin should be discontinued immediately and appropriate treatment given. Drugs that inhibit peristalsis must not be given.

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

Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (ie sunburn-like skin reactions) occurs.

Tendonitis and/or rupture of tendons (which mainly affects the Achilles tendon) are observed during treatment with quinolone antibiotics These reactions are especially observed in elderly patients and patients treated with corticosteroids. At the first sign of pain or inflammation, ciprofloxacin should be discontinued and the affected extremity should be made non-weight-bearing.

Because ciprofloxacin has some activity against *Mycobacterium tuberculosis*, false-negative cultures may occur when specimens are obtained during ciprofloxacin treatment.

Ciprofloxacin should be used with caution in patients with myasthenia gravis.

Studies in immature animals showed ciprofloxacin may cause arthropathy in weight-bearing joints. However, review of safety data in patients younger than 18 years (mainly cystic fibrosis patients) revealed no signs of drug related damage to cartilage or joints.

In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome), the sodium content of Ciprofloxacin should be taken into account. Refer to Section 6.1, List of Excipients for sodium chloride content.

4.5. Interaction with other medicinal products and other forms of interaction

Xanthine derivative

Concurrent administration of ciprofloxacin and theophylline may cause increased plasma concentrations of theophylline. This may lead to theophylline-induced undesirable effects, which in very rare cases are left threatening. During concurrent administration of theophylline, plasma concentrations should be monitored, and the theophylline dose should be adjusted adequately. On concurrent administration of ciprofloxacin and caffeine or pentoxifylline, raised serum concentrations of these xanthine derivatives were reported.

NSAIDs
Animal trials have shown that concurrent administration of high doses of a quinolone and certain non-steroidal anti-inflammatory drugs (NSAIDs) (but not acetylsalicylic acid) may provoke convulsions.

Cyclosporin
A transient increase in the concentration of plasma creatinine is seen when ciprofloxacin and cyclosporin are administered simultaneously. Plasma creatinine concentrations should be checked regularly in these patients.

Anticoagulants
Simultaneous administration of ciprofloxacin and coumarin anticoagulants, such as warfarin, may increase the effect of the anticoagulant.

Glibenclamide
Simultaneous administration of ciprofloxacin and glibenclamide may increase the effect of glibenclamide

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

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

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.

Premedicants
It is recommended that opiate premedicants (eg papaveretum) or opiate premedicants used with anticholinergic premedicants (eg atropine or hyoscine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced. Co-administration of ciprofloxacin and benzodiazepine premedicants has been shown not to affect ciprofloxacin plasma levels. However, since decreased clearance of diazepam with a prolonged half-life has been reported during co-administration of ciprofloxacin and diazepam, and in an isolated case with midazolam, careful monitoring of benzodiazepine therapy is recommended.

Ropinirole
A potential for increased plasma levels of ropinirole with possible increase in adverse effects exists. In case of combined use, increased clinical monitoring and dosage adjustment of ropinirole may be required.

Other CYP1A2 substrates
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (eg theophylline, clozapine, tacrine, ropinirol, tizanidine). Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations, especially of theophylline, may be necessary.

In a crossover study, 10 healthy subjects were given ciprofloxacin 500mg or placebo twice daily for three days, at the end of which a single dose of tizanidine 4mg was given. There was an increase in tizanidine serum concentrations (Cmax increase: 7-fold, range: 4 to 21 fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with

ciprofloxacin compared to placebo. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (refer to Section 4.3)

4.6 Pregnancy and Lactation

Pregnancy
Use during pregnancy is contraindicated. As with other quinolones, ciprofloxacin has been shown to cause arthropathy in immature animals and, therefore, its use in pregnancy is contraindicated.

Administration to nursing mothers is contraindicated since quinolones administered at therapeutic doses are excreted in breastmilk in quantities that can be expected to affect the infant.

4.7. Effects on ability to drive and use machinery

Ciprofloxacin can alter the capacity for reactions to an extent that impairs the ability to drive a vehicle, to operate machinery or to work safely, particularly it taken in conjunction with alcohol.

4.8. Undesirable effects

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

The following undesirable effects have been observed:

Effects on the gastro-intestinal tract
Common (>1/100, <1/10): Nausea, diarrhoea, vomiting, digestive disorders, abdominal pain, flatulence, loss of appetite
Rare (>1/10,000, < 1/1,000): pseudomembranous colitis.

Effects on the nervous system
Common (>1/100, <1/10): dizziness, Headache, tiredness, agitation, tremor, confusion
Very rare (< 1/10,000): Insomnia, paraesthesia, sweating, ataxia, convulsive seizures (the spasmodic threshold in epilepsy may be reduced), increased intracranial pressure, anxiety states, nightmares, distress, depression, hallucinations.
In isolated cases: psychotic reactions (involving in some cases a risk of self-injury). These reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, Ciprofloxacin is t be discontinued immediately and the treating physician informed.

Effects on sensory organs
Very rare (< 1/10,000): dysgeusia and dysosmia as well as possible loss of the sense of smell, which normally recovers after the end of the therapy, disturbed vision (eg diplopia, chromatopsia), tinnitus, transient (especially high frequency) hearing loss.

Hypersensitivity reactions
The following reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, Ciprofloxacin is to be discontinued immediately and the treating physician informed.
Common (>1/100, <1/10): skin reactions such as rash, pruritus, drug fever.

Very rare (< 1/10,000):
- punctiform cutaneous bleeding (petechiae), vesicles with haemorrhage (haemorrhagic bullae) and small nodules (papules) with crust formation showing vascular involvement (vasculitis), urticaria, erythema nodosum, erythema multiforme (mild to very severe forms ie Stevens-Johnson syndrome), Lyell syndrome
- Interstitial nephritis, hepatitis, and hepatic necrosis to life-threatening hepatic failure
- Anaphylactic/anaphylactoid reactions (eg ranging from facial, vascular and laryngeal oedema, through to dyspnoea and shock), in some cases with the first dose of the medicinal product. If such reactions occur, Ciprofloxacin is to be discontinued immediately, and medical treatment for shock should be given.

Effects on the cardiovascular system
Uncommon (> 1/1,000, <1/100): palpitation
Very rare (< 1/10,000): peripheral oedema, hot flushes, migraine, fainting, tachycardia.
Effects on the locomotor apparatus
Uncommon (> 1/1,000, <1/100): arthralgia and joint swelling
Very rare (< 1/10,000): muscle pains, inflammation of the tendon sheaths (tenosynovitis).
In isolated cases: tendonitis and torn tendons (eg of Achilles' tendon) may occur during treatment with fluoroquinolones. These events were observed predominantly among older patients who had been systematically treated beforehand with corticosteroids. If tendonitis is suspected, treatment with Ciprofloxacin must be discontinued immediately, physical effort avoided and, if necessary, medical treatment initiated. Aggravation of the sympthoms of myasthenia gravis.

Effects on the blood and blood compnents
Uncommon (> 1/1,000, <1/100): eosinophilia, leucopenia, granulocytopenia, anaemia, thrombocytopenia.
Very rare (< 1/10,000): leucocytosis, thrombocytosis, haemolytic anaemia, pancytopneia, agranulocytosis, altered prothrombin values.

Influence on laboratory values/urinary sediment
Patients with liver damage in particular may show a transient rise in transaminases and alkaline phosphatase or even cholestatic jaundice; a transient increase in serum urea, creatinine or bilirubin.
In isolated cases: hyperglycaemia, crystalluria or haematuria.

Others
Uncommon (> 1/1,000, <1/100): pulmonary embolism, dyspnoea, pulmonary oedema, epistaxis, hemoptysis and hiccough.
Very rare (< 1/10,000): asthenia, a transient impairment of kidney function to transient renal failure.
Photosensitivity: it is recommended that patients avoid long lasting exposure to sunlight or irradiation with UV-light (solarium) during treatment with ciprofloxacin; treatment should be discontinued in cases of photosensitivity reactions (eg skin reactions similar to sun burn).

Long term and repeated use of Ciprofloxacin can lead to superinfections with resistant bacteria or fungi.

4.9. Overdose

Based on the limited information available in two cases of ingestion of over 18g of ciprofloxacin, reversible renal toxicity has occurred. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and

acidify, if required, to prevent crystalluria. Patients must be kept well hydrated and, in the case of renal damage resulting in prolonged oliguria, dialysis should be initiated.

Serum levels of ciprofloxacin are reduced by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones
ATC Code: J01 MA 02

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

Mechanism(s) of resistance
Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all 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 physicochemical properties of the various active substances within the class and the affinity of transport systems for each active substance.

Breakpoints:
According to EUCAST the following breakpoints for aerobic bacteria have been defined for ciprofloxacin:
- Enterobacteriaceae: ≤0.5 μg/ml for susceptible, >1 μg/ml for resistant;
- Pseudomonas spp. ≤0.5 μg/ml for susceptible, >1 μg/ml for resistant;
- Acinetobacter spp. ≤1 μg/ml for susceptible, >1 μg/ml for resistant;
- S. pneumoniae ≤0.125 μg/ml for susceptible, >2 μg/ml for resistant;
- Staphylococcus spp. ≤1 μg/ml for susceptible, >1 μg/ml for resistant;
- H. influenzae and M. catarrhalis ≤0.5 μg/ml for susceptible, >0.5 μg/ml for resistant;

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

Commonly susceptible species
<u>Gram-negative aerobe species</u>
Haemophilus influenzae
Moraxella catarrhalis
Morganella morganii
Proteus mirabilis
Proteus vulgaris

<u>Anaerobes</u>
Peptococcus spp.

Peptostreptococcus spp.
Veillonella parvula

Other pathogens
Legionella pheumophila

Species for which acquired resistance may be a problem
Gram-positive aerobes
Coagulase-negative Staphylococcus
Staphylococcus aureus*
Streptococcus agalactiae
Streptococcus pneumoniae+
Streptococcus pyogenes+

Gram-negative aerobes
Acinetobacter spp.
Enterobacter spp.
Escherichia coli
Klebsiella pneumoniae
Klebsiella oxytoca
Pseudomonas aeruginosa
Serratia marcescens

Other pathogens
Chlamydia spp.+

Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.

Gram-negative aerobes
Stenotrophomonas maltophila

Anaerobes
Bacteroides fragilis group

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

+ might be regarded as being of intermediate susceptibility to ciprofloxacin.

Ciprofloxacin is not considered the active substance of first choice for treatment of infections with anaerobes or staphylococci and streptococci.

5.2. Pharmacokinetic properties

Absorption:
After oral administration, ciprofloxacin is predominantly absorbed from the deuodenum and upper jejunum and reaches peak serum concentrations within 60-90 min. After single doses of 250mg and 500mg C_{max} values are about 0.8-2.0 mg/l and 1.5-2.9 mg/l respectively. The absolute bioavailability is approximately 70 to 80%. C_{max}– and AUC- values are proportionally increased with the dose.

Distribution:
The steady-state volume of distribution of ciprofloxacin is 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma in non-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravascular space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.

Metabolism/Elimination
Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5 ml/min/kg, and total clearance amounts to 8-10 ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.
Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 show antibacterial activity comparable with or smaller than nalidixic acid. M4 with the lowest quantity has an antimicrobial activity very much corresponding to norfloxacin.
Up to 70% of a parenteral dose may be excreted unchanged in urine within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 15% of an intravenous dose.
Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.
The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral and after intravenous administration.
Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renal function must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

Paediatrics
The pharmacokinetics of ciprofloxacin in children with cystic fibrosis differs from that in children without cystic fibrosis, and dosing recommendations are only applicable for children with cystic fibrosis.
Intravenous administration of 10mg/kg three times daily or oral administration of 20mg/kg twice daily to children with cystic fibrosis gives an exposure that is comparable to that in adults following an oral dose of 750mg twice daily.

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

Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of Ciprofloxacin in vitro and in animal experiments in comparison with other fluoroquinolones.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients
Lactic Acid
Sodium Chloride (900 mg/100ml equivalent to 154 mmol sodium per litre),
Concentrated Hydrochloric Acid

Water for Injections

6.2. Incompatibilities

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

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

Solutions containing ciprofloxacin should not be mixed with or added to solutions containing other agents than listed below (see section 6.6).

6.3. Shelf life

Unopened polypropylene bag:
Two years.

From a microbiological point of view, the product should be used immediately on opening.

6.4 Special precautions for storage

Unopened polypropylene bag:
Store below 25°C. Keep the bag in the outer carton.

Since Ciprofloxacin 2 mg/ml Solution for Infusion is light-sensitive, the bags should always be stored in the cardboard outer container. No special precautions are required during the normal 30 - 60 minute infusion period. If the product is inadvertently removed from the outer carton, the stability of the product is maintained for a period of up to three days in daylight.

Do not refrigerate or freeze Ciprofloxacin 2 mg/ml Solution for Infusion. If the 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 the product.

6.5 Nature and contents of container

100 ml polypropylene bags:
Plastic bags of polypropylene of 100 ml, with rubber (type I) closures, and Aluminium caps with plastic flip-top covers. The bags are placed in cartons.
Boxes of 10 bags.

200ml polypropylene bags:
Plastic bags of polypropylene of 200 ml, with rubber (type I) closures, and Aluminium caps with plastic flip-top covers. The bags are placed in cartons.
The bags are placed in cartons.
Boxes of 5 bags.

6.6 Instructions for use and handling

Intravenous infusion:
The use of freshly prepared solutions is recommended (see section 6.3).

Ciprofloxacin should not be mixed with other drug products which are chemically or physically unstable at pH of 3.9 - 4 .5 (see section 6.2).

The solution should be clear. Do not use if particles are present.

Ciprofloxacin is compatible with the following commonly used infusion fluids: Ringer's solution, Ringer lactate solution, 0.9% Sodium chloride solution, Dextrose 5% and Dextrose 10% solutions, Fructose 10% solution Sodium chloride 0.45% + Dextrose 5% solution and Sodium chloride 0.225% + Dextrose 5% solution. All solutions are stable for 48 hours below 25°C, with the only exception of the mixture of Ciprofloxacin with Ringer solution, which is stable for 12 hours below 25°C.

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

7. MARKETING AUTHORISATION HOLDER

Noridem Enterprises Ltd., (trading as Brownes)
Evagorou & Makariou,
Mitsi Building 3, Suit.115,
1065 Nicosia, Cyprus.

8. MARKETING AUTHORISATION NUMBERS

PL 24598/0009

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/10/2006

10. DATE OF REVISION OF THE TEXT

03/10/2006

Patient Information Leaflet

Ciprofloxacin 2 mg/ml Solution for Infusion

Ciprofloxacin

Please read all of this leaflet carefully. It includes important information on how you should take this medicine correctly and safely.

- Keep this leaflet. You may need to read it again.
- If you are the parent of a child who is to be given this medicine, read the leaflet replacing "you" with "your child" throughout.
- The medicine is prescribed only for you, and you should 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 get serious, or you notice any side effects not listed in the leaflet, please tell your doctor, nurse or pharmacist.
- If you have further questions, please ask your nurse, doctor or pharmacist.

The name of your medicine is Ciprofloxacin 2mg/ml Solution for Infusion

In the rest of this leaflet Ciprofloxacin 2mg/ml solution for infusion is called Ciprofloxacin.

In this leaflet:

1. What Ciprofloxacin is and what it is used for

Ciprofloxacin is type of medicine called an antibiotic. Antibiotics work by killing the bacteria (germs) that cause an infection. If the infection is not treated by your medicine, the bacteria (germs) can continue to grow in your body. This will make you feel very unwell, and could even be life-threatening.

Ciprofloxacin works by killing some types of bacteria. Your doctor will decide if Ciprofloxacin is the right antibiotic to treat your infection.

Ciprofloxacin is used to treat infections caused by bacteria (germs) including infections of:

- the lungs and breathing airways including certain types of pneumonia.
- the ear and the sinuses (nose)
- the urinary tract (such as your bladder or tubes leading to your kidneys)
- the genital (sex) organs, including gonorrhoea and inflammation of the prostate in men
- the pelvic organs (this is the area between your hip bones)
- intra-abdominal organs (this is the belly area),
- typhoid fever (this infection can be caused by food poisoning)
- the skin and soft tissue (such has wound infections)
- the bones and joints
- severe blood infections (your doctor or nurse may call this septicaemia or blood poisoning)
- children and teenagers (between 5 and 17 years old) who have cystic fibrosis and get a lung infection caused by a germ called P. aeruginosa.

The doctor or nurse giving you this medicine will ask some questions about you. They need the following information before you have this medicine for the first time.

Do not take Ciprofloxacin

- If you are allergic to this medicine, or any other quinolone or fluoroquinolone antibiotic (such as levofloxacin, nalidixic acid, norfloxacin, ofloxacin or moxifloxacin)
- If you have had problems with your tendons when you have taken other fluoroquinolone medicines
- If you are pregnant or you are breastfeeding
- If you are a child or teenager (between 5 and 17 years old) who does *not have* cystic fibrosis and worsening problems with your lungs
- If you are a child younger than 5 years old
- If you are taking a medicine called tinazidine.

Do not take Ciprofloxacin if any of the above statements are true.

Take special care with Ciprofloxacin

Before your treatment starts, tell your doctor or nurse if:

- You have epilepsy, or if you have ever had other problems related to the nerves connecting to your brain
- You have a family history of, or you have the inherited condition called Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- You have a condition called myasthenia gravis (this is a rare disorder where the muscles become very weak and tired)
- You are on a low sodium (salt) diet.

During or after treatment make sure to tell your doctor or nurse immediately:

- If you think you are getting an allergic reaction to your medicine (even if it is your first dose)
- If you have any new pain or discomfort when passing urine. It is important to drink plenty of liquid while having this medicine to help prevent tiny crystals forming in your urine.
- If you get severe and continuing diarrhoea which may contain blood. These symptoms may mean that you are suffering from a condition called pseudomembranous colitis
- If your skin becomes more sensitive to sunlight or UV light (a reaction like sunburn). You should avoid strong sunshine and sun-bed treatments.
- If you get pain and swelling around your tendons (such as around your ankles), especially if you are elderly (over 65 years old), or taking one of a group of medicines called corticosteroids. You should also rest the painful area.

Please read the next page of this leaflet

Taking other medicines

Please tell your doctor about any medicines you may be taking or have recently been taking. Remember also any medicines you may be taking that do not need a prescription.

If you are taking any of the following medicines, it is very important to tell your doctor:

- Anticoagulant drugs such as warfarin for making the blood thinner (may make the anticoagulant drug work more)
- Cyclosporin (may affect your kidneys for a short time).
- Glibenclamide (may make your blood sugar levels drop too low)
- Mexiletine (may make the amount of mexiletine in your blood too high)
- Non-steroidal anti-inflammatory drugs also called NSAIDs (may cause fits or seizures). You may take Aspirin.
- Phenytoin (may make the amount of phenytoin in your blood too high).
- Premedicants (medicines you get before an operation) such as papaveretum, atropine, hyoscine, diazepam and midazolam (may make the amount of Ciprofloxacin in your blood too low)
- Probenecid (may make the amount of Ciprofloxacin in your blood too high).
- Ropinirole (may give you more side effects)
- Theophylline, caffeine or pentoxyfilline (may give you more side effects)
- Tinazidine (your doctor will not give you Ciprofloxacin with this medicine as you may get more side effects such as low blood pressure and become very sleepy)

- Other medicines such as clozapine, tacrine (may make the amount of these medicines in your blood too high).

Your doctor may want to carry out some extra blood tests if you are taking any of these medicines to check that your medicines are working together correctly.

Pregnancy and breastfeeding
- If you are pregnant, or think you may be pregnant you must tell your doctor as ciprofloxacin has a risk of causing problems with the baby's joints.
- If you are breastfeeding, you must tell your doctor as the ciprofloxacin will be in the breastmilk and may affect your baby.

Your doctor will not give you this medicine during pregnancy and breastfeeding.

Driving and using machines
You should not drive or operate machinery while taking ciprofloxacin as it can make you dizzy and affect your sight, especially if you have been drinking alcohol.

Important information about some of the ingredients of Ciprofloxacin
If you are on a low sodium diet, it is important to know how much sodium is in your medicine.
Each bag of 100 ml (millilitres) of this medicine contains 15.4 millimoles (mmol) of sodium.
Each bag of 200ml contains 30.8 mmol of sodium.

3. How to take Ciprofloxacin

A doctor or a nurse will usually give you this medicine.

Your doctor or nurse will give you the correct dose as a drip into your vein (your doctor or nurse may call this an IV or intravenous infusion). This may take between 30 and 60 minutes depending on the amount you are getting.

Your doctor will decide the amount (dose) of your medicine to give you. This will depend on a number of things. These things include how bad your infection is, the type of infection and the type of bacteria causing it, your body weight, your age and how well your kidneys are working.

Your doctor will also decide how long you need to take your medicine for. This will depend on how bad your infection is and how you respond to your medicine. The usual time is 5 to 7 days. Longer treatment may be needed for a chronic (long-term) or severe infections where you will need to stay on your medicine for an extra 3 days after you feel better.

For children and teenagers with cystic fibrosis (between 5 and 17 years old) being treated for a lung infection, you will need to stay on your medicine usually for 10 to 14 days.

Adults and elderly (over 65 years old):
The usual dose is 100 to 400 milligram (mg) twice daily (two times during the day) as an intravenous infusion (drip).

Doses for other infections are:
- Gonorrhoea: 100 mg as a single dose (one dose only)
- Urinary tract infections: 100 mg twice daily
- Adult patients with cystic fibrosis who get lung infections: 400 mg twice daily
- Other adult infections: 200 to 400 mg twice daily.

Children with cystic fibrosis between 5 and 17 years old with a lung infection:
The usual dose is 10 mg per kg of bodyweight three times daily. The medicine will be given to you as an intravenous infusion (drip) which will take 60 minutes.

Patients with severe kidney problems:
Your doctor may give you a half dose if you have severe problems with your kidneys. Your doctor may also want to test your blood to decide on the best dose for you.

If you take more Ciprofloxacin than you should
A doctor or a nurse will usually give you this medicine. If you think you may have received too much medicine, please tell your doctor or nurse at once.

Too much ciprofloxacin in your blood will cause kidney problems. Please read carefully the important advice at the beginning of the next section, Section 4, about how to spot the signs of too much ciprofloxacin in your blood.

If you forget to take Ciprofloxacin
A doctor or a nurse will usually give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

If you stop taking Ciprofloxacin
It is very important to finish the course of treatment your doctor has prescribed, even if you start to feel better. If you do not finish the course of treatment, your infection may get worse again.

If you have further questions on the use of your medicine, ask your doctor, nurse or pharmacist.

Please read the next page of this leaflet

4. Possible side-effects

Like all medicines, Ciprofloxacin can cause side effects, but not everyone gets them. The expected benefit of your medicine will usually be greater than the risk of you suffering any harmful side effects.

The chance of you having a side effect is described using words and numbers in this section.

Important: Side effects or symptoms to look out for, and what to do if you are affected.
The first signs of having too much Ciprofloxacin in your blood are problems with your kidneys such as pain or discomfort passing urine and pain in your belly area. If these symptoms occur you must seek urgent medical advice.

Other side effects which need urgent medical attention:
If get any one of the following reactions you must tell your doctor or nurse immediately and your medicine will be stopped.

The following are common side effects. They probably affect up to 1 in 10 people taking Ciprofloxacin:
- skin rash, itching, high temperature.

The following are very rare side effects. They probably affect up to 1 in 10 000 people:
- small red spots on your skin which bleed, large blisters filled with blood, severe rash, sores and ulcers on your skin which may become serious and even life-threatening
- Problems with your kidneys and liver which may get worse and may be life-threatening
- Severe allergic reactions can sometimes happen with the first dose of Ciprofloxacin and can cause swelling of your face, throat and veins. This can lead to painful breathing and difficulty with breathing. You may go into shock and your reaction may be life-threatening. **Your doctor or nurse will also give you medical treatment for shock.**

In isolated (once-off) cases:
- your tendons may tear (such as around your ankles), especially if you are elderly (over 65 years old), or taking one of a group of medicines called corticosteroids.
- you may have feelings where you want to or have already tried to physically harm yourself.

If get any of the above reactions you must tell your doctor immediately and your medicine will be stopped.

Other possible side effects:
The following are common side effects probably affecting up to 1 in 10 people taking this medicine:

- nausea (feeling sick), diarrhoea, vomiting, stomach problems, pain in your belly, wind, loss of appetite
- dizziness, headache, tiredness, agitation, tremor (your limbs may shake), confusion

The following are uncommon side effects probably affecting fewer than 1 in 100 people:
- fast or abnormal heartbeats
- pain and swelling of your joints
- you may have fewer blood cells (which can make you feel tired, look pale, you can bruise or bleed easier or you may get more infections).
- you may get a blood clot in your lungs which can affect your breathing, painful breathing, swelling in your lungs, nose bleeds, you may spit up blood, hiccups,

The following are rare side effects probably affecting fewer that 1 in 1 000 people:
- severe and continuing diarrhoea which may contain blood (your doctor or nurse may call this pseudomembranous colitis).

The following are very rare side effects probably affecting fewer than 1 in 10 000 people:
- difficulty sleeping, tingling or numbness in your hands or feet, sweating, difficulty with your muscles, fits or seizures, pressure in your head, anxiety, nightmares, distress, depression, hallucinations
- a bad taste in your mouth, a bad smell or no sense of smell, eyesight problems, ringing in your ears or short-term loss of your hearing
- swelling of your limbs (such as arms and legs), hot flushes, migraine, fainting, faster heartbeats
- muscle pains, inflammation of your tendons
- very high or very few blood cells in your blood. This can make you can look pale, feel very tired, have a higher chance of getting infections, bruise or bleed easier and your skin or eyes will look yellow (jaundice).
- weakness, short-term problems with your kidneys which may become serious, reaction to sunlight or UV light like sunburn. You should avoid strong sunshine and sun-bed treatments. **If this happens, you must tell your doctor or nurse as soon as possible and your medicine will be stopped.**

In isolated (once-off) cases:
- if you have a condition called myasthenia gravis (where your muscles become very weak and tired), this may get worse.

If you use ciprofloxacin quite often or for a long time, you can get other infections that ciprofloxacin cannot work against properly.

If any of these side effects gets serious or if you notice any troublesome symptoms which you think may be side effects, please tell your doctor, nurse or pharmacist.

Please read the next page of this leaflet

5. How to store Ciprofloxacin

Your doctor, nurse or pharmacist will usually store your medicine for you.

Keep your medicine out of the reach and sight of children.

Do not use your medicine after the expiry date (EXP) given on the carton and the label on the plastic container (bag). The expiry date is the last day of the month written on the packaging.

Store below 25ºC. Do not put your medicine in the fridge or in the freezer as crystals may form if the medicine gets too cold. If you see crystals in your medicine, do not use the medicine and tell your doctor, nurse or pharmacist immediately.

Always keep your medicine in the outer carton to protect it from light because it is sensitive to light.

Open it and use it straight away.

Your medicine should not be mixed with certain other medicines that may also be given by infusion. Please ask your doctor, nurse or pharmacist if you want any more information about this.

Give any leftover medicine to your doctor, nurse or pharmacist. If you do this, it will help protect the environment. Do not put it down the drain or in the dustbin.

6. Further information

What Ciprofloxacin contains

The active medicine is Ciprofloxacin lactate.
Each 100 ml (millilitre) bag will contain 200 mg (milligram) of ciprofloxacin. Each 200 ml bag will contain 400 mg of ciprofloxacin.

The other ingredients are Lactic acid, Sodium Chloride, concentrated Hydrochloric Acid and Water for Injections.

What Ciprofloxacin looks like and contents of the pack

Ciprofloxacin is a solution for infusion. This means it is ready to give to you in a plastic bag as an intravenous or IV infusion (drip).

Each bag of Ciprofloxacin contains 100 ml or 200 ml of your medicine.
100 ml bags come in boxes of 10.
200ml bags come in boxes of 5.

Marketing Authorisation Holder and Manufacturer

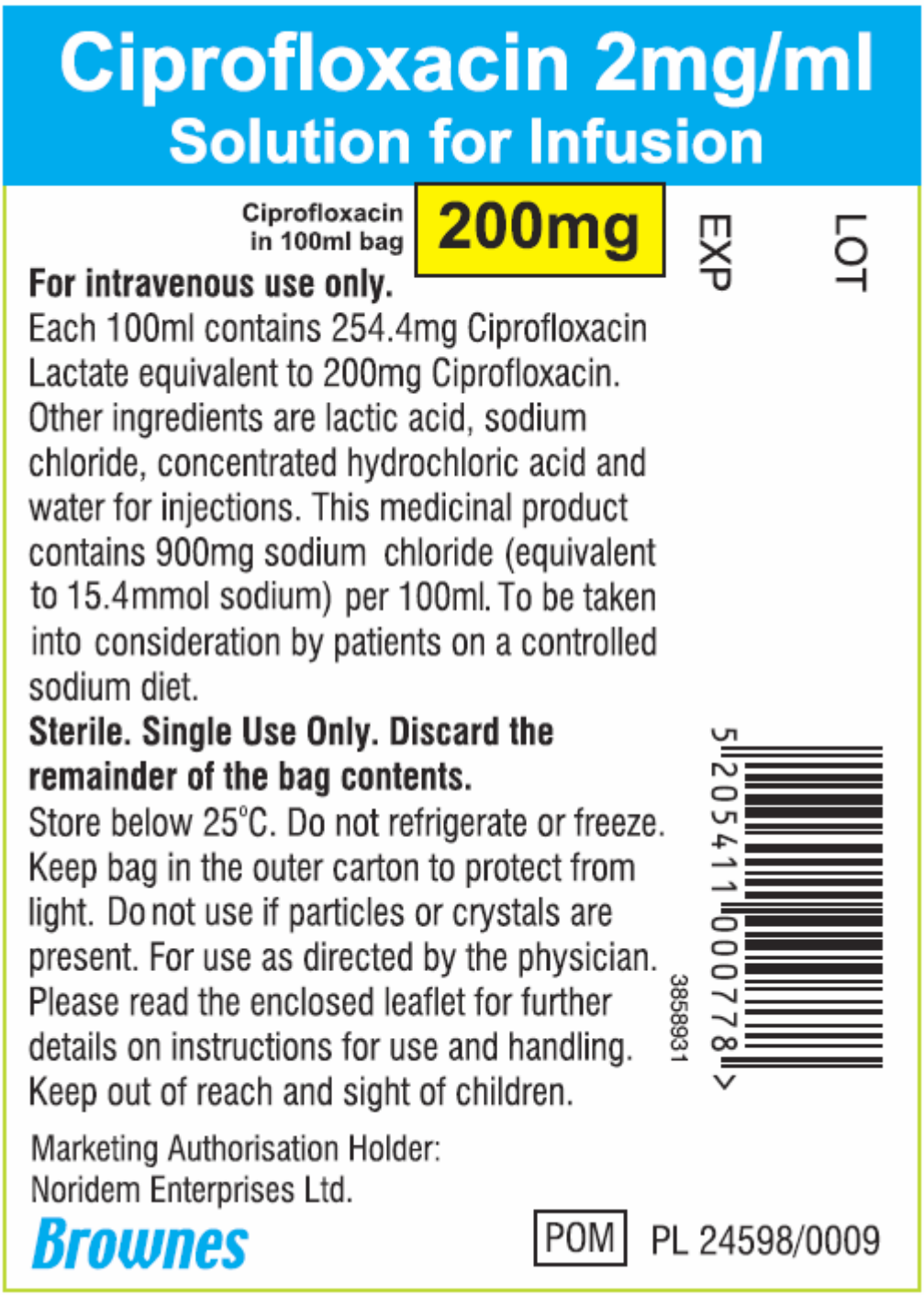
Marketing Authorisation Holder: Noridem Enterprises Ltd., Evagorou & Makariou, Mitsi Building 3, Suit.115 1065 Nicosia, Cyprus.
Manufacturer: Demo S.A., 21st km National Road Athens, Lamia, 14568 Athens, Greece.

This leaflet was prepared in July 2006

If this leaflet is difficult to see or read please contact the following address for help:
Brownes, Pincent's Kiln Industrial Park, Reading, RG31 7SB, United Kingdom

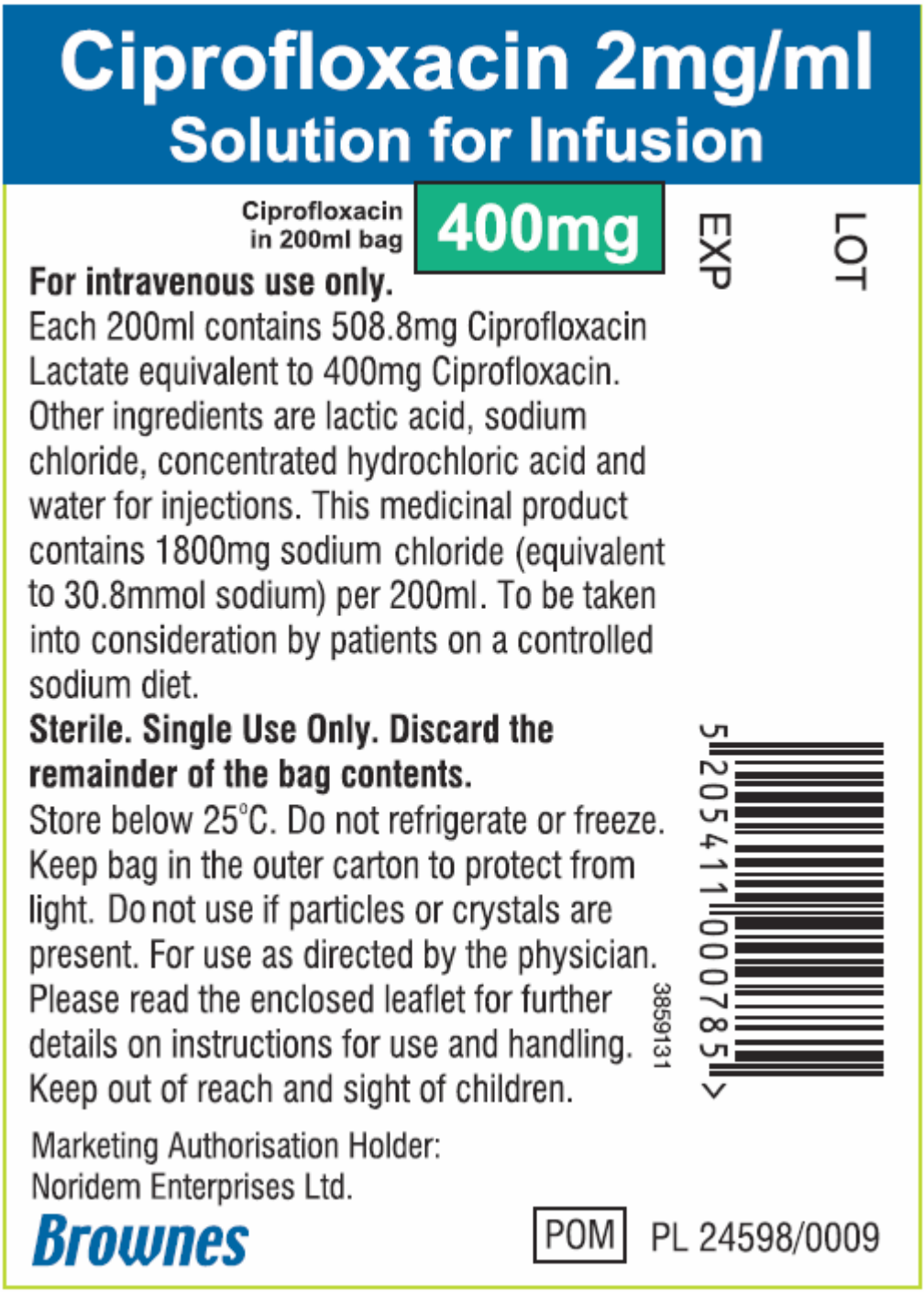
PACKAGING

100 ml:



Ciprofloxacin 2mg/ml
Solution for Infusion
200mg
Ciprofloxacin in 100ml bag
For intravenous use only
10 bags x 100ml
BARCODE
LOT :
EXP :
Browne's
ΔΙΑΣΤΑΣΕΙΣ: 895mm X 391mm
PANTONE PROCESS CYAN CVC
BLACK
YELLOW
Manufactured by:
DEMO S.A.
Athens, Greece
Marketing Authorisation Holder:
Norbrook Laboratories Limited
Evagorou & Makariou
Mitsi Building 3, Suit 115
1065 Nicosia, Cyprus
POM
PL 24598/0099
Each 100ml contains 254.4 mg ciprofloxacin lactate
equivalent to 200mg ciprofloxacin.
Other ingredients: Lactic acid, Sodium Chloride (15.4mmol sodium per 100ml), Hydrochloric acid and Water for injections.
Store below 25°C.
Keep the bag in the outer carton to protect from light.
No special storage precautions are required during the normal 30-60 minute infusion period.
Do not refrigerate or freeze.
Do not use if particles are present.
Do not use if crystals are present.
If the product is refrigerated, crystals may form. These crystals will redissolve at room temperature and do not adversely affect the quality of the product
Do not mix with other drugs which are unstable at pH of 3.5-4.5.
Please read the enclosed leaflet for further details on instructions for use and handling. Please read the enclosed patient information leaflet.
Use as directed by the physician.
Single use only. Discard the remainder of the bag contents after use.
KEEP OUT OF SIGHT AND REACH OF CHILDREN

200 ml:


Ciprofloxacin 2mg/ml
Solution for Infusion
Ciprofloxacin in 200ml bag
400mg
EXP
LOT
For intravenous use only.
Each 200ml contains 508.8mg Ciprofloxacin Lactate equivalent to 400mg Ciprofloxacin. Other ingredients are lactic acid, sodium chloride, concentrated hydrochloric acid and water for injections. This medicinal product contains 1800mg sodium chloride (equivalent to 30.8mmol sodium) per 200ml. To be taken into consideration by patients on a controlled sodium diet.
Sterile. Single Use Only. Discard the remainder of the bag contents.
Store below 25°C. Do not refrigerate or freeze. Keep bag in the outer carton to protect from light. Do not use if particles or crystals are present. For use as directed by the physician. Please read the enclosed leaflet for further details on instructions for use and handling. Keep out of reach and sight of children.
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Marketing Authorisation Holder:
Noridem Enterprises Ltd.
Brownes
POM
PL 24598/0009

ΔΙΑΣΤΑΣΕΙΣ: 895mm X 391mm
PANTONE 3405 CVC
PANTONE 301C
BLACK
Ciprofloxacin 2mg/ml
Solution for Infusion
400mg
Ciprofloxacin
in 200ml bag
For intravenous use only
5 bags x 200ml
LOT :
EXP :
BARCODE
Browne's
Each 200ml contains 808.8 mg ciprofloxacin lactate
equivalent to 400mg ciprofloxacin.
Other ingredients: Lactic acid, Sodium Chloride (80.8mmol sodium per 200ml), Hydrochloric acid and Water for injections.
Store below 25°C.
Keep the bag in the outer carton to protect from light.
No special storage precautions are required during the normal 30-60 minute infusion period.
Do not refrigerate or freeze.
Do not use if particles are present.
Do not use if crystals are present.
If the product is refrigerated, crystals may form. These crystals will redissolve at room temperature and do not adversely affect the quality of the product.
Do not mix with other drugs which are unstable at pH of 3.5-4.5.
Please read the enclosed leaflet for further details on instructions for use and handling. Please read the enclosed patient information leaflet.
Use as directed by the physician.
Single use only. Discard the remainder of the bag contents after use.
KEEP OUT OF SIGHT AND REACH OF CHILDREN
Marketing Authorisation Holder:
Norbdem Enterprises Limited
Evagorou & Makariou
Mitsi Building 3, Suit 115
1065 Nicosia, Cyprus
Manufactured by:
DEMO S.A.
Athens, Greece
POM
PL 24598/0009