CIPROFLOXACIN 2MG/ML INFUSION
PL 20568/0003

UKPAR

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CIPROFLOXACIN 2MG/ML INFUSION

PL 20568/0003

LAY SUMMARY

The MHRA granted Claris Lifesciences UK Limited a Marketing Authorisation (licence) for the medicinal product Ciprofloxacin 2mg/ml Infusion (PL 20568/0003), on the 11th of September 2006. This prescription only medicine (POM) is an oral antibiotic approved for the treatment of many common bacterial infections.

Ciprofloxacin 2mg/ml Infusion contains the active ingredient Ciprofloxacin, which is an oral antibiotic approved for the treatment of many common bacterial infections.

The data presented to the MHRA, pre licensing, demonstrated that Ciprofloxacin 2mg/ml Infusion is equivalent to the originator product/UK reference product Ciproxin 0.2% w/v Infusion (PL 00010/0150), which was first authorised on 3rd February 1987 and is currently marketed by Bayer.

No new or unexpected safety concerns arose from this application. It was, therefore, judged that the benefits of taking Ciprofloxacin 2mg/ml Infusion outweigh the risks. Hence a Marketing Authorisation has been granted.

CIPROFLOXACIN 2MG/ML INFUSION

PL 20568/0003

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 2mg/ml Infusion to Claris Life sciences UK Limited on the 11th September 2006. This product is a prescription only medicine.

This is a National Complex Abridged application for Ciprofloxacin 2mg/ml Infusion made under Article 10.1(a)(iii) of Directive 2001/83/EC. The originator product/UK reference product is Ciproxin 0.2% w/v Infusion (PL 00010/0150) which was first authorised on 3rd February 1987 and is currently marketed by Bayer. The application is therefore valid.

This product contains the active ingredient Ciprofloxacin 2mg/ml Infusion and is indicated for the treatment of infections caused by sensitive bacteria:

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 first choice for the treatment of pneumococcal pneumonia.
- the ear and 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 tissues.
- 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 use of antibacterial agents.

Ciprofloxacin 2mg/ml Infusion contains the active ingredient Ciprofloxacin, which 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.

PHARMACEUTICAL ASSESSMENT

PL NUMBER: **PL 20568/0003**

PRODUCT: **Ciprofloxacin 2mg/ml Infusion**

ACTIVE: **Ciprofloxacin (as lactate)**

COMPANY: **Claris Life sciences Limited.**

E.C. ARTICLE: **10.1(a)(iii) first paragraph**

LEGAL STATUS: **POM**

I. REQUESTS FOR INSPECTION ACTION PRIOR TO AUTHORISATION

The proposed finished product manufacturing facility has been inspected by the MHRA. Satisfactory evidence of GMP compliance has been provided.

II. INTRODUCTION

This is a National Complex Abridged application for Ciprofloxacin 2mg/ml Infusion made under Article 10.1(a)(iii) of Directive 2001/83/EC. The originator product/UK reference product is Ciproxin 0.2% w/v Infusion (PL 00010/0150) which was first authorised on 3rd February 1987 and is currently marketed by Bayer. The application is therefore valid.

The proposed name of the product is considered acceptable.

III. DRUG SUBSTANCE

The applicant cross refers to a Drug Master File for Ciprofloxacin Lactate.

The finished product manufacturer's drug substance specification has been provided

IV. DRUG PRODUCT

IV.1 Description and Composition of the Drug Product

The proposed composition is included below:

Ingredient	Ref to std
Ciprofloxacin (as lactate)	In-house
Lactic acid	Ph.Eur.
Sodium chloride	Ph.Eur.
Hydrochloric acid	Ph.Eur.
Water for injections	Ph.Eur.

The ratio between ciprofloxacin and lactic acid is in-line with recommendations of the USP monograph for ciprofloxacin injection. The excess of lactic acid is comparable to the UK reference product.

The products are presented in USP type II glass containers which are sealed with grey siliconised bromobutyl rubber closures and plastic flip-off caps. Each bottle has a plastic hanger for use during administration.

IV.2 Pharmaceutical Development

IV.2.1 Components of the Drug product

IV.2.1.1 Drug Substance

The product contains ciprofloxacin lactate. There is no Ph.Eur monograph for ciprofloxacin lactate and quality is controlled using an in-house specification. Compatibility studies demonstrated ciprofloxacin is compatible with the proposed excipients.

IV.2.1.2 Excipients

The product incorporates conventional, compendial excipients.

IV.2.2 Drug Product

IV.2.2.1 Formulation development

The proposed formulation is comparable to the UK reference product and the applicant has provided evidence of isotonicity. The formulation is stable and no significant changes were noted on exposure to heat. The applicant has provided comparative batch analysis data (3 batches) for the proposed product and the UK reference product (2 batches). The two products are of comparable quality and impurity profiles were similar.

IV.2.2.2 Overages

There is no drug substance overage.

IV.2.2.3 Physicochemical and biological properties

Physicochemical properties of the drug substance are described in the DMF assessment report. As the product is administered parenterally a bioequivalence study was not required.

IV.2.3 Manufacturing Process Development

A summary of the method of manufacture has been provided. The applicant has also demonstrated that terminal sterilisation in an autoclave does not effect key properties of the solution for infusion including pH and ciprofloxacin assay.

IV.2.4 Container Closure System

The container-closure system is described above (see IV.1). Use of USP Type II glass containers is acceptable provided that the containers also comply with Ph.Eur. requirements for Type I or Type II glass (see IV.7). The applicant states that protection of the finished product is sufficient, as evident from stability test results.

Rubber stoppers are tested against (and comply with) the Type I requirements of the Ph.Eur (see IV.7 below) and are therefore considered acceptable. Extraction studies have also been completed by the rubber stopper supplier in water (pH 3, neutral and pH 11) and isopropanol. Samples were tested for stearic acid/palmitic acid, hexane, phenolic antioxidants, halogenated

oligomers, metal ions (Mg, Ca, Zn, Si, Ti, Al), sulphur, chlorides and bromides, t-amyl phenol, total sulphur and polybutene.

IV.2.5 Microbiological Attributes

The product is terminally sterilised. It is intended for single dose use and does not contain any preservatives.

IV.2.6 Compatibility

The applicant states that ciprofloxacin infusion is incompatible with injection solutions which are chemically unstable at pH 3.9-4.5 (e.g. penicillins, heparin solution). This is consistent with advice included in the SmPC for the UK reference product.

All samples complied with the requirements of the finished product specification over the duration of study. The results are considered supportive of the claims made in sections 6.2 and 6.6 of the SmPC regarding compatibility of co-infusion solutions.

IV.3 Manufacture

IV.3.1 Manufacture(s)

The proposed manufacturer is stated.

IV.3.2 Batch Formula

The applicant has provided the batch formula which is a linear scale-up of the proposed unit composition.

IV.3.3 Description of Manufacturing Process and Process Controls

A satisfactory description of the manufacturing process and process controls has been provided.

IV.3.4 Control of Critical Steps and Intermediates

Details of the critical steps and intermediates have been provided.

IV.3.5 Process Validation and/or Evaluation

Validation studies conducted by the applicant are acceptable.

IV.4 Control of Excipients

The applicant states that sodium chloride, lactic acid, hydrochloric acid and water for injections are controlled against the requirements of their corresponding Ph.Eur. monographs.

The applicant has confirmed that the product does not contain any excipients of human or animal origin.

IV.5.1 Specification(s)

The proposed finished product specification has been provided by the applicant.

The proposed finished product specification complies with the requirements of the Ph.Eur. general monograph for parenteral presentations and with the requirements of the BP monograph for Ciprofloxacin intravenous infusion. Additional tests for extractable volume, sodium chloride content and lactic acid content are acceptable. The proposed limits for lactic acid content are in-line with USP requirements for ciprofloxacin injection.

IV.5.2 Analytical Procedures

Analytical methodology has generally been adequately described.

IV.5.3 Validation of Analytical Procedures

Appropriate validation of analytical procedures has been described.

IV.5.4 Batch Analyses

Exemplary batch analysis results have been provided for three production scale batches (each presentation). All batches complied with the proposed finished product specification.

IV.5.5 Characterisation of Impurities

With the exception of the ethylene diamine analogue, no impurities were present above the identification threshold.

IV.5.6 Justification of Specification(s)

The proposed drug substance specification has been justified based on the requirements of the BP monograph for ciprofloxacin infusion, the USP monograph for ciprofloxacin infusion and current guidelines. The proposed finished product specification is considered adequate for routine control of the product.

IV.6 Reference Standards or Materials

Certificates of analysis have been provided.

IV.7 Container Closure System

Glass containers: The finished product manufacturer's specifications have been provided which consist of appropriate visual and dimensional tests. The applicant states throughout the application that USP type II glass containers are used.

Rubber stoppers: The applicant has provided specifications for rubber stoppers. Rubber stoppers are generally tested against Ph.Eur. requirements for rubber closures and exemplary batch analysis results have been provided.

IV.8 Stability

IV.8.1 Stability Summary and Conclusion

Stability test results have been provided for commercial scale batches.

Based on the results provided the applicant has proposed a shelf-life of 24 months when stored at a temperature not exceeding 25°C. As no significant changes were observed under accelerated conditions (see below) this storage precaution is not critical but may be retained by the applicant.

In line with details registered for the cross-reference product containers should not be refrigerated and should be protected from light. These requirements have not been discussed by the applicant. However, appropriate warnings have been included in section 6.4 of the proposed SmPC.

IV.8.2 Post-approval Stability Protocol and Stability Commitment

The applicant has confirmed that an additional one batch per year will be included in stability studies (real time and accelerated).

IV.8.3 Stability Data

Batches were tested against stability indicating tests included in the finished product specifications. Tolerance limits were the same as for release. No significant changes were observed.

Relative humidity used during intermediate stability studies (67.5%) did not comply with ICH requirements. However, as no significant changes were observed under accelerated storage conditions this is not considered critical.

V. APPENDICES

Adventitious Agents Safety Evaluation

No materials of animal origin are included in the finished product. Lactic acid is chemically synthesised.

REGIONAL INFORMATION

The applicant has provided the MHRA's specific national data requirements including a summary of the proposed method of manufacture, the finished product specification and the drug substance specification.

VII ASSESSOR'S COMMENTS ON THE SPC, LABELS AND PACKAGE LEAFLET

PIL - satisfactory
Label – satisfactory

VII.1 Other information

VII.1.2 Bioavailability, bioequivalence

As the proposed products are to be administered parenterally, a bioequivlance study is not required.

VII.1.4 Essential similarity

The proposed product is qualitatively and quantitatively identical to the UK reference in terms of active substance and is administered via the same route. Criteria for essential similarity have been fulfilled.

VII.2.1 Administrative

VII.2.2 Comment on Expert report

The quality expert has provided a summary of Module 3. His CV has been provided and he is considered sufficiently qualified for his responsibilities.

VII.2.3 MAA form

The MAA form is satisfactory

VII.2.4 GMP

The applicant has demonstrated the requisite standards of GMP

VII.2.5 Guideline Compliance

The applicant has generally complied with current guidelines.

VIII ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation should be granted.

Pharmaceutical Assessor
October 2005
July 2006

PRECLINICAL ASSESSMENT

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

CLINICAL ASSESSMENT

PL NUMBER:	**20568/0003**
PRODUCT:	**Ciprofloxacin 2mg/ml Infusion**
ACTIVE:	**Ciprofloxacin**
COMPANY:	**Claris lifesciences (UK) limited**
LEGAL STATUS:	**POM**

I. INTRODUCTION

- This is a National Complex Abridged application for Ciprofloxacin 2mg/ml Infusion made under Article 10.1(a)(iii) of Directive 2001/83/EC. The originator product/UK reference product is Ciproxin 0.2% w/v Infusion (PL 00010/0150) which was first authorised on 3rd February 1987 and is currently marketed by Bayer.
- The original product quoted is **Bayer's Ciproxin 0.2% W/V Intravenous infusion,** first authorised on 3/02/1987, PL number provided is 00010/0150 (which is provided in section 1.4.2 under Article 10.1 (a)(i) – so called "informed consent application").
- Since this is an intravenous preparation, no bioequivalence study is presented by the applicant.

I.1 GCP aspects

No new clinical trials are presented in this application; hence no statement about GCP compliance is available.

I.2 Orphan Medicinal Products

Not applicable

I.3 Therapeutic Class

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.

I.4 Background

Antimicrobial activity

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.

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.

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.

I.5 Regulatory Status

Ciprofloxacin for intravenous use was first approved in the UK in 2/02/1987, MA was granted to Bayer Plc (PL 00010/0149), trade name Ciproxin solution 1.0% w/v subsequently renewed on 14/05/1997. A second MA was granted to Bayer for intravenous Ciprofloxacin (PL 00010/0150) under the trade name of Ciproxin Infusion 0.2% W/V, approved also on 3/02/1987 and renewed on 14/12/1992.

The applicant has the same product approved or under registration in a number of countries outside the EEA.

I.6 Indications

The proposed indications are in line to those laid out in the SPC of the original product.

I.7 Dose and Dose Regimen

These are in line with those in the approved SPC of the original product.

I.8 Consideration for Paediatric use

The proposed SPC estates that paediatric use is not generally recommended, except in inhalation anthrax and cystic fibrosis patients with lung infections caused by *Pseudomona aeruginosa*.

I.9 Assessor's Comment

The application form is acceptable

II. CLINICAL PHARMACOLOGY

II.1 Pharmacokinetics

The basic pharmacokinetics of ciprofloxacin have been summarised in the SPC. Since this application pertains to intravenous administration only, no bioequivalence study against the reference product is required.

II.2 Pharmacodynamics

Effectively, the pharmacodynamics of ciprofloxacin relate to its antibacterial activity. There were no new data presented. The Pre-clinical and Clinical Expert reports briefly present the results of literature searches.

III CLINICAL EFFICACY

Ciprofloxacin is already approved for use in its intravenous form in multiple countries including the UK. The short Clinical Overview does not provide any new data regarding efficacy.

IV. CLINICAL SAFETY

The applicant presents in brief the results of a literature search highlighting .the possible interaction between Ciprofloxacin and ropinirole, and with clozapine and N-desmethylclozapine. The mechanism proposed is that of inhibition of the liver isoenzyme CYP1A2. The applicant does not recommend amending the SPC but further monitoring.

VI. CLINICAL EXPERT REPORT

The clinical expert report author is acceptable, they are currently a general practitioner, clinical assistant in ophtalomology and Company Medical Advisor.

VIII.1 PRODUCT LITERATURE

VIII.1.1 SPC

The SPC is acceptable

VIII.1.2 PIL

The PIL is acceptable

VIII.1.3 Labels

The labels are acceptable

VIII.1.4 Comments on application form (if appropriate)

The application form is acceptable

IX. CONCLUSIONS

A Marketing Authorisation may be granted.

Medical Assessor
31/08/2006

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Ciprofloxacin 2mg per ml 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 have been supplied with these applications and none are required for applications of this type.

EFFICACY

The basic pharmacokinetics of ciprofloxacin have been summarised in the SPC. Since this application pertains to intravenous administration only, no bioequivalence study against the reference product is required.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that of the reference product.

RISK BENEFIT ASSESSMENT

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

CIPROFLOXACIN 2MG/ML INFUSION

PL 20568/0003

STEPS TAKEN FOR ASSESSMENT

1	The MHRA received the marketing authorisation application on 08/02/2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 23/02/2005
3	Following assessment of the application the MHRA requested further information relating to the dossier on and 18/11/2005, 07/03/2006, 31/03/2006, 14/07/2006, 11/09/2006
4	The applicant responded to the MHRA's requests, providing further information relating to the dossier on 21/02/2006, 24/03/2006, 22/05/2006, 29/08/2006, 31/08/2006
5	The application was determined on 11/09/2006

CIPROFLOXACIN 2MG/ML INFUSION

PL 20568/0003

STEPS TAKEN AFTER ASSESSMENT

Date submitted	Application type	Scope	Outcome

CIPROFLOXACIN 2MG/ML INFUSION

PL 20568/0003

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2mg/ml Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

50ml pack size:	127.2 mg Ciprofloxacin lactate equivalent to100mg Ciprofloxacin
100ml pack size:	254.4mg Ciprofloxacin lactate equivalent to 200mg Ciprofloxacin
200ml pack size:	508.8mg Ciprofloxacin lactate equivalent to 400mg Ciprofloxacin

For a full list of excipients see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Ciprofloxacin is indicated for the treatment of the following infections caused by sensitive bacteria:

Adults:

Treatment of the following infections when caused by ciprofloxacinsensitive pathogens:

Infections of

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

- 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 use of antibacterial agents.

4.2. Posology and method of administration

Posology
The dosage 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 recommendations are provided as a guideline and refer to intravenous dosing only (Note that different recommendations apply to oral administration of ciprofloxacin.

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

The following dosages are recommended for specific types of infection:

Table 1 : Recommended Adult Dosage

Indication	**Treatment dosage i.v. (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 adjustment of dosage is necessary.

Children and adolescents (5 – 17 years):

10mg/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 >265 micromole/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 of Treatment

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), 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 dose (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 intravenous infusion.

4.3. Contraindications

Ciprofloxacin is contraindicated 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 fluoro quinolone 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, therapy should be discontinued immediately

In patients with epilepsy or other lesions of the central nervous system (e.g. reduced convulsion threshold, a history seizures, diminished blood flow, changes in 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.

There is a risk of pseudomembranous colitis with broad-spectrum antibiotics possibly leading to a fatal outcome. It is important to consider this in patients suffering from severe, persistent diarrhoea. With ciprofloxacin this effect has been reported rarely. If pseudomembranous colitis is suspected treatment with ciprofloxacin should be stopped and appropriate treatment given (e.g. oral vancomycin). 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 (i.e., 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 in 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.

Sodium chloride content

This product contains 9 mg/ml of sodium chloride corresponding to 15.4 mmol (or 354 mg) of sodium per 100ml.

This should be taken into consideration for patients on a low sodium diet.

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

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

NSAIDs
Animal trials have shown that concurrent administration of high doses of 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 cyclosporine are administered simultaneously. Plasma concentration should be checked regularly in these patients.

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

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

Probenecid
Probenecid inhibits the renal excretion of ciprofloxacin, resulting in an increased in the plasma concentration 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 (e.g.papaveretum) or opiate premedicants used with anticholinergic premedicants (e.g. 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 have 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 exits. In case of combined use, increased clinical monitoring and dosage adjustment of ropinirole may be required.

Tizanidine
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.

4.6. Pregnancy and lactation

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 breast milk in quantities that can be expected to affect the infant.

4.7. Effects on ability to drive and use machines

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 if 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 to be discontinued immediately and the treating physician informed.

Effects on sensory organs

Very rare (<1/10,000): dysgeusia and dysosmia as well as a possible loss of the sense of smell, which normally recovers after the end of the therapy, disturbed vision (e.g. 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-induced 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 multiforme (mild to very severe forms i.e. Stevens Johnson syndrome), Lyell syndrome. Intestinal nephritis, hepatitis, and hepatic necrosis to life threatening hepatic failure.
Anaphylactic/anaphylactoid reactions (e.g. 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): muscular pains, inflammation of tendon sheaths (tenosynovitis).
In isolated cases: tendonitis and torn tendons (e.g. of Achilles' tendon) may occur during treatment with fluoroquinolones. These events were observed predominantly among older patients who had been systemically 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 symptoms of myasthenia gravis.

Effects on the blood and blood components
Uncommon (>1/1,000, <1/100):, eosinophilia, leucopenia, granulocytopenia, anemia thrombocytopenia.
Very rare (<1/10,000): leucocytosis, thrombocytosis, haemolytic anaemia, pancytopenia, 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 term exposure to sunlight or irradiation with UV light (solarium) during treatment with ciprofloxacin; treatment should be discontinued in cases of photosensitivity reactions (e.g. skin reactions similar to sun burn).

Long term and repeated use of ciprofloxacin can lead to super-infections 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

Mechanisim of action

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

Mechanisms of resistance

In-vitro investigations have shown that resistance to Ciprofloxacin is commonly due to mutations in bacterial topoisomerases and usually develops slowly and gradually ("multistep" type).

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.

Breakpoints

EUCAST: S $\leq$ 0.5µg/ml, R $\geq$1 µg/ml

Susceptibility
The prevalence of acquired resistance can vary for some species geographically and with time Therefore it is important to obtain local information on local resistance patterns, particularly when treating more severe infections. The information provided below gives only approximate guidance as to whether microorganisms will be susceptible to ciprofloxacin or not. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Commonly susceptible species

Gram-negative aerobes
Aeromonas hydrophila
Brucella melitensis
Citrobacter freundii
Enterobacter spp.
Escherichia coli
Haemophilus influenzae
Moraxella catarrhalis
Morganella morganii
Plesiomonas shigelloides
Proteus mirabilis
Proteus vulgaris
Providencia spp.
Shigella spp.
Vibrio spp.
Yersinia enterocolitica

Anaerobes
Peptococcus spp.
Peptostreptococcus spp.
Veillonella parvula

Other pathogens
Legionella pneumophila

Species for which acquired resistance may be a problem

Gram-positive aerobes
Staphylococcus aureus (methicillin sensitive)
*Staphylococcus aureus (methicillin resistant)**
Streptococcus pneumoniae+
Streptococcus pyogenes+

Gram-negative aerobes
Acinetobacter spp.
Klebsiella spp.
Neisseria gonorrhoeae
Pseudomonas aeruginosa

Serratia spp.

Other pathogens
Chlamydia spp.+

Inherently resistant organisms

Gram-positive aerobes
Enterococcus spp

Gram-negative aerobes
Stenotrophomonas maltophila
Flavobacterium meningosepticum
Nocardia asteroides

Anaerobes
Bacteroides fragilis
Bacteroides thetaiotaomicron
Clostridium difficile

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

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). Following intravenous administration of ciprofloxacin, the mean maximum plasma concentrations were achieved at the end of the infusion period. That is, for a 100mg or 200mg dose, 30 minutes, and for a 400mg dose, 60 minutes. Reported plasma levels at this time point were 1.8mg/l, 3.4mg/l and 3.9mg/l, respectively.

Ciprofloxacin is widely distributed and has a high volume of distribution within 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). Four different antimicrobially active metabolites have been reported, desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxaciprofloxacin (M3) and formylciprofloxacin (M4). M2 and M3 account for one third each of metabolised substance and M1 is found in small amounts (1.3-2.6% of the

dose). M4 has been found in very small quantities (<0.1% of the dose). M1-M3 have antimicrobial activity comparable to nalidixic acid and M4 found in the smallest quantity has antimicrobial activity similar to that of norfloxacin.

Elimination of ciprofloxacin and its metabolites occurs rapidly, primarily by the kidney. After single oral and intravenous doses of ciprofloxacin, 55% and 75% respectively are eliminated by the kidney and 39% and 14% in the faeces within 5 days. 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. Renal clearance is between 0.18-0.3 l/h.kg and total body clearance between 0.48-0.60 l/h.kg. Approximately 1% of a ciprofloxacin dose is excreted via the biliary route. 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. A total body clearance of approximately 35l/h was observed after intravenous administration.

Some studies carried out with ciprofloxacin in patients with severe renal insufficiency (serum creatinine>265 micromole/l or creatinine clearance <20ml/minute) demonstrated either a doubling of the elimination half-life, or fluctuations in half-life in comparison with healthy volunteers. It is recommended that in severely renally impaired patients, the total daily dose should be reduced by half, in patients with severe renal insufficiency, although monitoring of drug serum levels provides the most reliable basis for dose adjustment as necessary.

Results of pharmacokinetic studies in paediatric cystic fibrosis patients have shown dosages of 20mg/kg orally twice daily or 10mg/kg I.V. three times daily are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimen.

5.3. Preclinical safety data

Following extensive oral and intravenous toxicology testing with ciprofloxacin, only two findings which may be considered relevant to the use of ciprofloxacin in man were observed. Crystalluria was noted in those species of animals which had a normally alkaline urine. Kidney damage without the presence of crystalluria was not observed. This effect is considered a secondary inflammatory foreign-body reaction, due to the precipitation of a crystalline complex of ciprofloxacin, magnesium and protein in the distal tubule system of the kidneys. This is considered not to be a problem in man, because the urine is normally acidic. However, to avoid the occurrence of crystalluria, patients should be well hydrated and excessive alkalinity of the urine avoided.

As with other quinolones, damage to the weight-bearing joints of only juvenile rats and dogs treated with ciprofloxacin was noted in repeat dose toxicity testing. This was more noticeable in the dog. Although analysis of available safety data from ciprofloxacin use in paediatric patients did not disclose any evidence of drug related cartilage or articular damage, the use of ciprofloxacin in children and growing adolescents is generally not recommended (with the exception of treatment of cystic fibrosis), unless the benefits are

considered to outweigh the potential risks. Additionally, because of the potential of arthropathy, the use of ciprofloxacin during pregnancy and lactation is not recommended.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactic Acid
Sodium Chloride
Hydrochloric Acid
Water for Injections

6.2. Incompatibilities

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

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

For compatible co-infusion solutions see Section 6.6- Instructions for Use/Handling

6.3. Shelf life

36 months

After opening, this product should be used immediately

6.4. Special precautions for storage

Store below 25ºC
Keep container in outer carton.
Do not refrigerate or freeze

If the product is inadvertently refrigerated, crystals mat form. Do not use if crystals are present

No special precautions are required during the 30 -60 minute administration period.

6.5. Nature and contents of container

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

Each outer carton contains one bottle.

6.6. Instruction for disposal

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

Claris Lifesciences UK Limited
Crewe hall
Crewe
Cheshire
CW1 6UL
UNITED KINGDOM

8. MARKETING AUTHORISATION NUMBER

PL 20568/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2006

10 DATE OF REVISION OF THE TEXT

07/09/2006

Patient Information Leaflet (UK)

Ciprofloxacin 2 mg/ml Infusion

Read all of this leaflet carefully before you start taking this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

The name of your medicine is Ciprofloxacin 2mg/ml infusion.
The active ingredient is Ciprofloxacin (as Ciprofloxacin Lactate).
Ciprofloxacin 2mg/ml infusion comes in 50ml, 100ml and 200ml vials containing 100mg, 200mg and 400mg Ciprofloxacin.

The 50ml vial contains 100mg of Ciprofloxacin (as the Lactate Salt).
The 100ml vial contains 200mg of Ciprofloxacin (as the Lactate Salt) and the 200ml vial contains 400mg of Ciprofloxacin (as the Lactate Salt).
Other ingredients are Lactic Acid, Hydrochloric Acid, Sodium Chloride and Water for Injections.

Marketing Authorization Holder:
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom.

Manufacturer:
Peckforton Pharmaceuticals Ltd.
Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom.

1. What Ciprofloxacin 2mg/ml infusion is and what it is used for

Ciprofloxacin belongs to a group of antibiotics called fluoroquinolones (or just called quinolones).
It works by killing some types of bacteria that can cause infections.
Ciprofloxacin is used to treat:
- Lung infections such as pneumonia.
- Infections of the ears or of the sinuses.
- Infections of the bladder and kidneys.
- Infections of the genital organs, including gonorrhoea (a sexually transmitted disease) and inflammation of the prostate gland in men (prostatitis).
- Infections in or around the uterus (womb) and tubes leading to the ovaries.
- Infections in the abdomen (belly) and gall bladder.
- Typhoid fever.
- Infections of the skin and spreading infections under the skin.
- Infections in the bones.
- Infections that have spread to the blood.

Ciprofloxacin may also be used for treating lung infections in children (aged five years or older) and teenagers who have cystic fibrosis.

2. Before you are given Ciprofloxacin 2mg/ml infusion

Ciprofloxacin is not suitable for everyone.
- You should not be given Ciprofloxacin if the answer to any of the following questions is **"YES". Ask your doctor or pharmacist if you are not sure about anything before you start to take Ciprofloxacin.**
- Are you or have you ever been told that you are allergic to Ciprofloxacin or other antibiotics of the same type (called fluoroquinolones or just quinolones)?
- Are you allergic to any of the other ingredients in Ciprofloxacin 2mg/ml infusion?
- Are you pregnant, do you think you may be pregnant or are you breastfeeding?
- Have you ever had problems with your tendons that were thought to be caused by a quinolone antibiotic?
- Are you less than 17 years old (unless you are being treated for cystic fibrosis)?
- Are you taking a medicine called tizanidine (this is used to treat spasticity associated with multiple sclerosis or injury or diseases of spinal cord)?
- Also, if it is your child who is to be treated, remember that Ciprofloxacin must not be used to treat children who are under five years old.

Ciprofloxacin may or may not be suitable for you if the answer to any of the following questions is "YES". Your doctor or pharmacist will advise if Ciprofloxacin is right for you.

- Do you have epilepsy or a condition that affects the nerves linked to the brain or the spinal cord (such as a history of stroke)? If so, Ciprofloxacin may increase your risk of having a fit.
- Do you or any members of your family have a deficiency in the blood enzyme called glucose-6-phosphate dehydrogenase (G6PD)? If Ciprofloxacin is taken it may lead to the break down of red blood cells, which can result in anemia and a yellowing of the skin (jaundice).
- Do you have a problem with weakness in your muscles called myasthenia gravis?
- Do you have problems with your kidneys and/or liver? Your doctor may reduce the dose if your kidneys and/or liver are not working properly.

While you are having Ciprofloxacin treatment

- You should not sunbathe or use UV tanning lamps because there is an increased risk of skin burning.
- You should avoid becoming dehydrated.

Ciprofloxacin can interfere with the results of laboratory tests for tuberculosis. If you have to have a test for tuberculosis while you are having Ciprofloxacin treatment, make sure that the doctor or nurse knows about your medicine.
If any of the above points apply to you now, was applied to you in the past, or if you are unsure about anything, please ask your doctor or pharmacist before you are given Ciprofloxacin.

Pregnancy and breast-feeding

Do not take Ciprofloxacin if you are pregnant, think you may be pregnant, or are breastfeeding. There is a risk that Ciprofloxacin may harm the growth of babies, before and after birth.

Driving or using machines

Ciprofloxacin may make you feel less alert, dizzy or confused, which may affect your ability to drive or operate machinery. This is more likely to happen at the start of treatment, when the dose is increased, when switching treatment or if you drink alcohol.

Taking other medicines

Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicines, even those not prescribed but obtained without a prescription.

Care is needed, if:

- you are taking theophylline, penotoxifylline or medicines that contain caffeine. Ciprofloxacin may increase blood levels of these medicines, which can cause problems such as fast heartbeat, sweating and agitation.
- you are taking certain painkillers known as non-steroidal anti-inflammatory drugs (NSAIDs). Some of these (e.g., ibuprofen) are in medicines that you can buy without a prescription. If these are taken with Ciprofloxacin, there may be an increased risk of fits.
- you are taking cyclosporin. Ciprofloxacin may increase the concentration of a substance called creatinine in your plasma and your doctor may take blood samples to monitor this.
- you are taking medicines that prevent the blood from clotting normally (anticoagulants) such as warfarin. Ciprofloxacin may increase the effect of warfarin.
- you are taking glibenclamide for diabetes. Ciprofloxacin may increase the effect of glibenclamide causing the blood sugar to fall to lower than unusual.
- you are taking probenecid. This increases the levels of Ciprofloxacin in the blood.
- you are taking mexiletine (a medicine used to treat disturbances in heart rhythm). Ciprofloxacin increase the blood levels of mexiletine.
- you are taking phenytoin for epilepsy. Ciprofloxacin may affect the blood levels of phenytoin so your doctor may take blood samples to check the levels.
- you are going to have a general anaesthetic. There are some medicines used before surgery that can reduce the blood level of Ciprofloxacin (including papaveretum and hyoscine), while Ciprofloxacin may cause an increase in blood levels of others (such as diazepam). You should make sure that you tell the doctor or dentist that you are taking Ciprofloxacin before you have a general anaesthetic.
- you are taking a medicine called ropinirole for Parkinson's disease. Ciprofloxacin may increase the blood levels of ropinirole increasing the possibility of side effects. Your doctor may adjust the dose of ropinirole.
- you take tizanidine for spasticity. You should not receive Ciprofloxacin. This is because Ciprofloxacin can increase the level of tizanidine in your blood resulting in side effects such as lowered blood pressure and sleepiness.
- you are on a low sodium diet. Ciprofloxacin 2mg/ml infusion contains 15.4 mmol/ (or 354mg) of sodium per 100ml. The total quantity of sodium administered to you during treatment will depend on the amount of medicine which you need and may range up to 61.6mmol (or 1416mg) per dose. This would need to be taken into consideration if you are on a sodium controlled diet and should be discussed with you doctor or nurse.

3. How Ciprofloxacin 2mg/ml infusion is given

Your doctor or nurse will ensure that you are given this medicine as prescribed by your doctor. The dose you are prescribed will depend on the type and severity of your infection. Your doctor will tell you how long your treatment with Ciprofloxacin will last.
Ciprofloxacin 2mg/ml infusion is given directly into a vein using a needle and plastic tubing (a "drip") over about 30 to 60 minutes, depending on the dose. There are some other solutions (such as penicillins or heparin solutions) that must not be given at the same time as Ciprofloxacin 2mg/ml infusion. Your doctor, nurse or pharmacist should check that you do not receive these other solutions.

Adults, including elderly people with normal kidneys

The usual adult dose is between 100 - 400mg twice daily.
- For most infections, it is usual to give 200 - 400mg twice daily.
- In infections of the bladder and kidney, the dose may be lower at 100mg twice daily.
- In gonorrhoea, 100mg as a single dose may be enough for simple infections but infections that have spread from the genital organs may need higher doses and may need to be treated for several days.

Kidney problems

If you suffer from severe kidney problems your doctor may reduce the dose or give you a single daily dose. If you are on haemodialysis or having continuous ambulatory peritoneal dialysis (CAPD) to treat kidney problems, special dosing instructions are needed.

Children and treatment with cystic fibrosis

For the treatment of lungs infection in people aged 5 to 17 years with cystic fibrosis, the dose is based on body weight. The usual dose is 10mg/kg three times daily (to a maximum daily dose of 1200mg).
Ciprofloxacin is not recommended for other infections in children, or in children less than 5 years old.
Your doctor may decide to stop treatment into a vein and ask you to continue treatment with Ciprofloxacin tablets. There will be a different dose and information leaflet supplied with the tablets. Make sure that you read that carefully. It is important that you keep taking Ciprofloxacin tablets until the prescribed course is finished. Do not stop taking the tablets just because you feel better. If you stop too soon, the infection may start up again.
If you still feel unwell at the end of your prescribed course of treatment, tell your doctor.
- If you think that you may have missed a dose of Ciprofloxacin, talk to your doctor, nurse or pharmacist.
- If you think that you may have been given more Ciprofloxacin than you should have, talk to your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, Ciprofloxacin 2mg/ml infusion can have side effects, although not everybody gets them. The most common side effects involve the gut and the nervous system.
If any of the following happen soon after receiving the infusion, tell you doctor or nurse immediately or go to the casualty department at your nearest hospital. These are very serious side effects. If you have them, you may have had a serious allergic reaction or other type of reaction to Ciprofloxacin. You may need urgent medical attention or, if you are not still in hospital, re-hospitalisation.
- Skin rash and itching: these effects occur in less than one in ten but more than one in a hundred persons.
- Peeling, blistering or crusting of the skin.
- Ulcers on the skin or in the mouth.
- Swelling of the face or neck.
- Breathing problems.
- Yellow coloration of the skin or the eyes.

These other effects occur in less than one in ten thousand persons.
You should also tell your doctor immediately and stop receiving Ciprofloxacin, if you notice:
- Pain or inflammation in the tendons. This effect occurs in less than one in ten thousand persons.
- Severe diarrhoea with bleeding or mucous. This effect occurs in less than one in a thousand but more than one in ten thousand persons.
- A feeling that you want to physically harm yourself. This only occurs in isolated cases.

Other possible side effects of Ciprofloxacin are:

<u>In less than one in ten but more than one in a hundred persons:</u>
- Feeling or being sick, indigestion, loss of appetite, flatulence (wind), pain in the belly, diarrhoea or loose stools.
- Fever.
- Dizziness, headache, tiredness, restlessness, uncontrolled shaking, confusion.

<u>In less than one in a hundred but more than one in a thousand persons:</u>
- Palpitation or increased heart rate.
- Blood clots in the lungs, breathlessness, nosebleeds, coughing up blood.

- Hiccoughs.
- Pain or swelling in the joints.
- Low numbers of some types of blood cells causing anaemia, increased risk of bleeding or increased risk of infections. Increased numbers of a type of blood cell called an eosinophil.

In less than one in ten thousand persons:
- Bleeding under the skin or into blisters.
- Hot flushes, migraine, fainting, swelling of the limbs, pains in the muscles.
- Inability to sleep (insomnia), pins and needles sensation, sweating, unsteadiness, fits, an increase in pressure around your brain, anxiety, nightmares, distress, depression, hallucinations.
- Disturbances in taste, loss of the sense of smell, disturbed vision, ringing in the ears (tinnitus), temporary hearing loss.
- Increased risk of sunburn.
- Problems with the liver or kidneys that lead to failure of these.
- Increase in some types of cells in your blood or in the cells that help blood to clot, decreases in all types of blood cells, changes in some blood proteins that are needed for normal clotting, anemia that is due to breaking up of red blood cells and occurs with yellowing of the skin and eyes.
- Increases in some blood chemicals that normally pass through the kidneys.
- Aggravation of the symptoms of myasthenia gravis.
- Increased blood sugar levels.
- Blood or crystals in your urine.

Some people develop thrush (a yeast infection of the vagina, mouth or skin folds) whilst they are taking antibiotics. You can get treatment for thrush from your doctor and treatment for vaginal thrush can be obtained from your pharmacist.

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

5. How Ciprofloxacin 2mg/ml infusion is stored

Your doctor, nurse or pharmacist will ensure that you do not receive Ciprofloxacin 2mg/ml infusion after the expiry date on the labelling.
Your doctor, nurse or pharmacist should ensure that the product is stored in the original container prior to use and will inspect the solution before it is used to make sure that it is not cloudy and that it does not contain any solids.
Ciprofloxacin 2 mg/ml infusion should be stored below 25°C. It should not be refrigerated or frozen as this may lead to the formation of crystals. If crystals are present the product should not be used.
Your doctor, nurse or pharmacist should ensure that Ciprofloxacin 2mg/ml infusion is stored out of the reach and sight of children.
The product is for single use and any remaining solution should be discarded.

Leaflet prepared: 09/2006

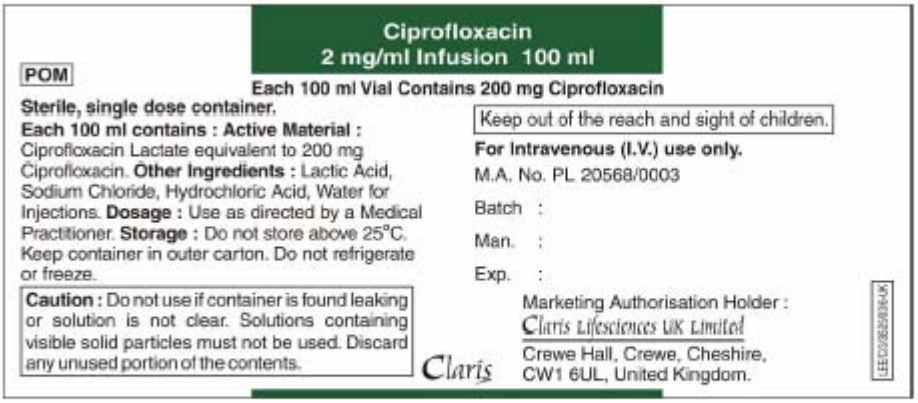
Claris

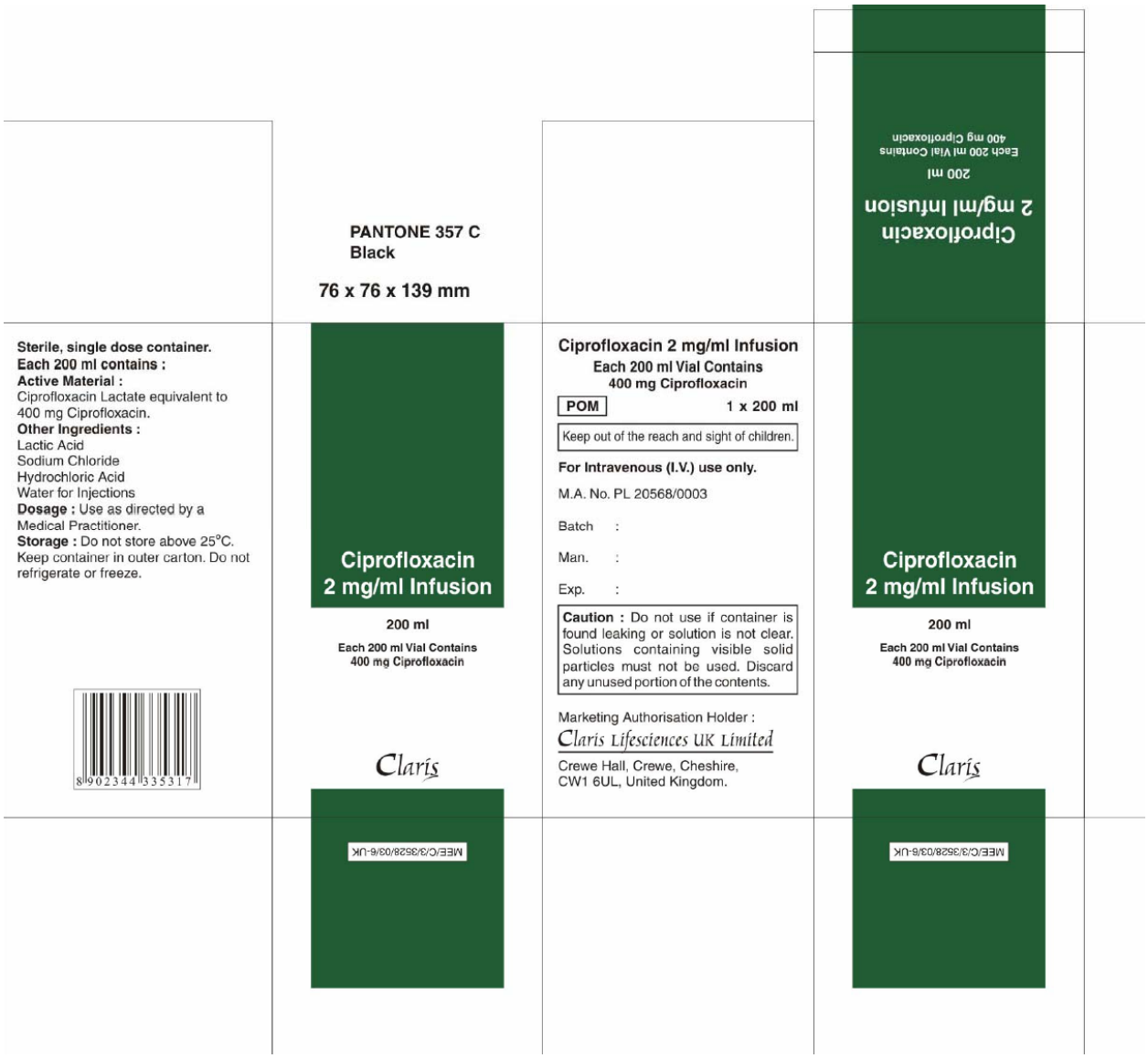
IEE:C:CiproNS1016-LX-PL

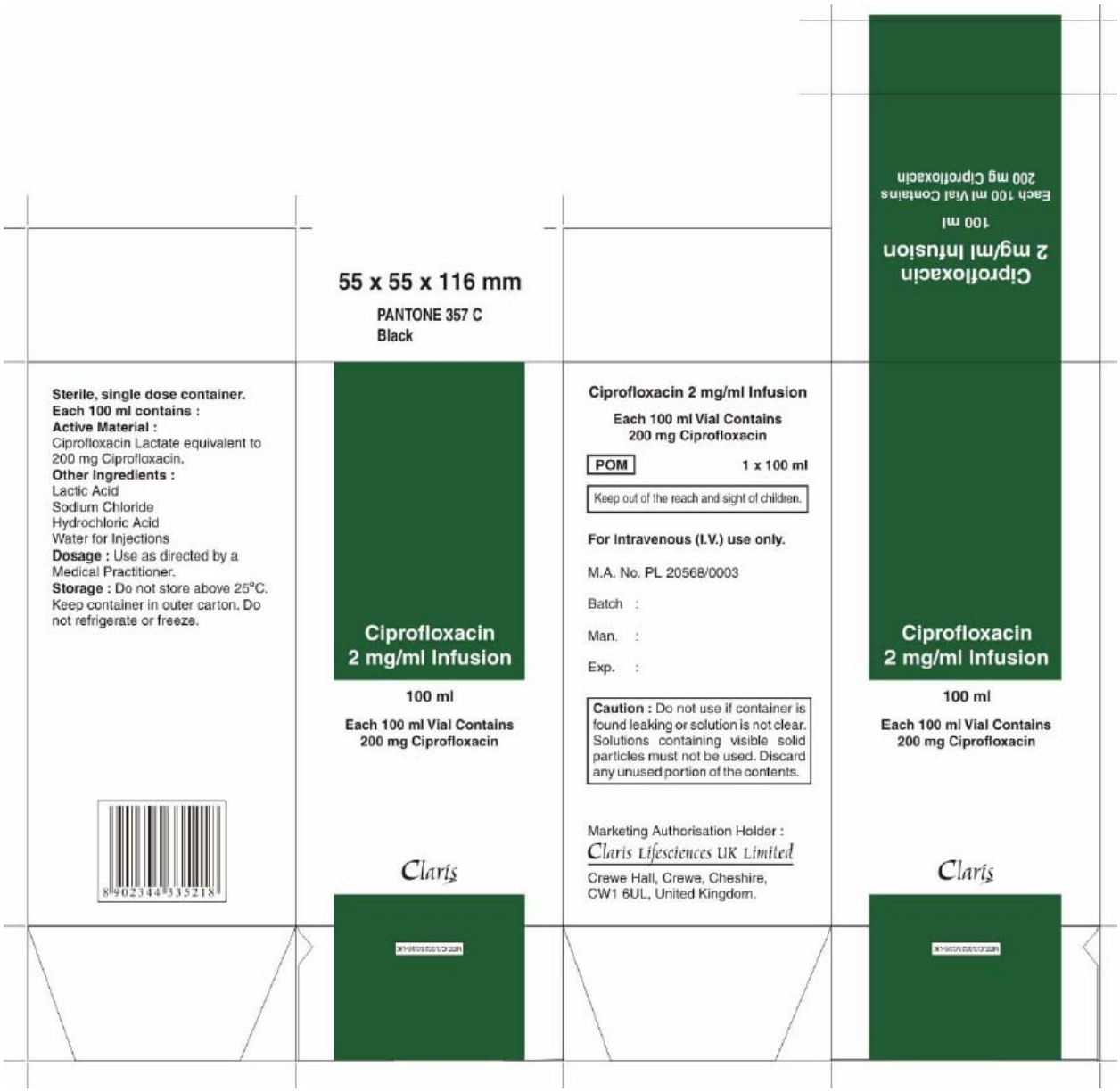
LABELLING

CIPROFLOXACIN (AS LACTATE) 0.2% W/V
INTRAVENOUS INFUSION

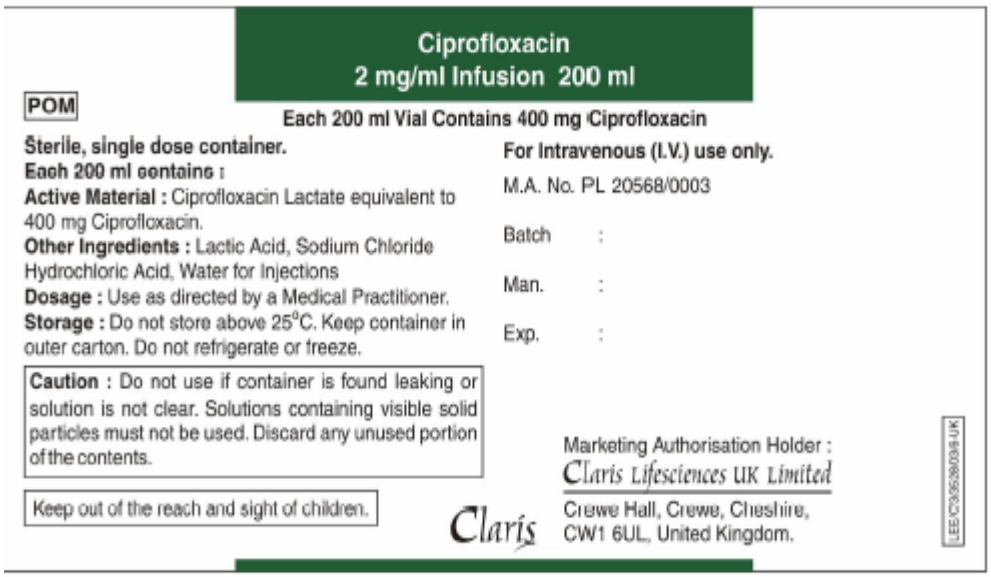
PL 20568/0003




PANTONE 357 C
Black
76 x 76 x 139 mm
Sterile, single dose container.
Each 200 ml contains :
Active Material :
Ciprofloxacin Lactate equivalent to 400 mg Ciprofloxacin.
Other Ingredients :
Lactic Acid
Sodium Chloride
Hydrochloric Acid
Water for Injections
Dosage : Use as directed by a Medical Practitioner.
Storage : Do not store above 25°C. Keep container in outer carton. Do not refrigerate or freeze.
8 902344 335317
Ciprofloxacin 2 mg/ml Infusion
200 ml
Each 200 ml Vial Contains 400 mg Ciprofloxacin
Claris
MEE/C/3/3528/03/6-UK
Ciprofloxacin 2 mg/ml Infusion
Each 200 ml Vial Contains 400 mg Ciprofloxacin
POM
1 x 200 ml
Keep out of the reach and sight of children.
For Intravenous (I.V.) use only.
M.A. No. PL 20568/0003
Batch :
Man. :
Exp. :
Caution : Do not use if container is found leaking or solution is not clear. Solutions containing visible solid particles must not be used. Discard any unused portion of the contents.
Marketing Authorisation Holder :
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom.
Ciprofloxacin 2 mg/ml Infusion
200 ml
Each 200 ml Vial Contains 400 mg Ciprofloxacin
Ciprofloxacin 2 mg/ml Infusion
200 ml
Each 200 ml Vial Contains 400 mg Ciprofloxacin
Claris
MEE/C/3/3528/03/6-UK

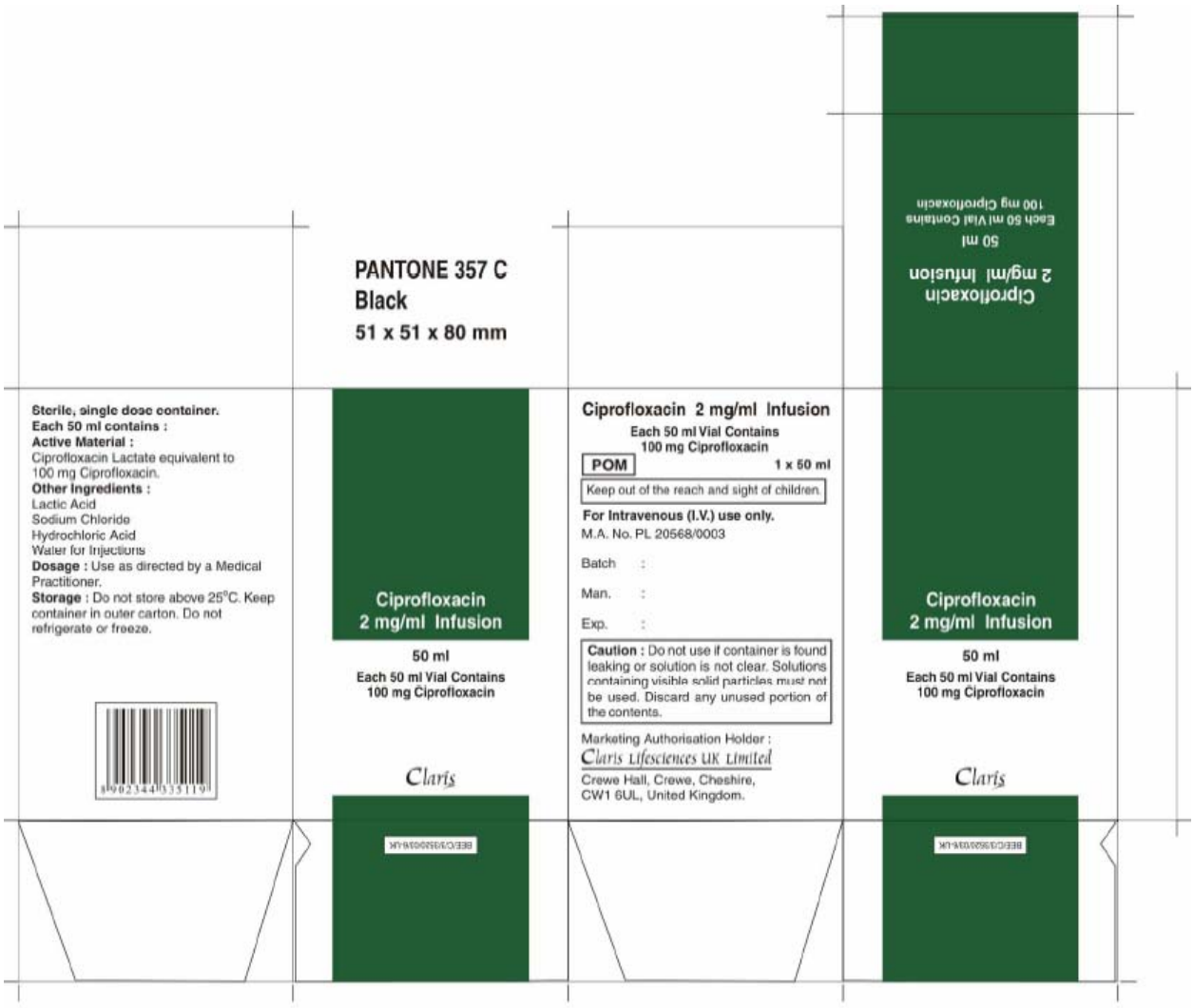

55 x 55 x 116 mm
PANTONE 357 C
Black
Sterile, single dose container.
Each 100 ml contains :
Active Material :
Ciprofloxacin Lactate equivalent to 200 mg Ciprofloxacin.
Other Ingredients :
Lactic Acid
Sodium Chloride
Hydrochloric Acid
Water for Injections
Dosage : Use as directed by a Medical Practitioner.
Storage : Do not store above 25°C. Keep container in outer carton. Do not refrigerate or freeze.
Ciprofloxacin 2 mg/ml Infusion
100 ml
Each 100 ml Vial Contains 200 mg Ciprofloxacin
Claris
Ciprofloxacin 2 mg/ml Infusion
Each 100 ml Vial Contains 200 mg Ciprofloxacin
POM
1 x 100 ml
Keep out of the reach and sight of children.
For Intravenous (I.V.) use only.
M.A. No. PL 20568/0003
Batch :
Man. :
Exp. :
Caution : Do not use if container is found leaking or solution is not clear. Solutions containing visible solid particles must not be used. Discard any unused portion of the contents.
Marketing Authorisation Holder :
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire, CW1 6UL, United Kingdom.
Claris
Ciprofloxacin 2 mg/ml Infusion
100 ml
Each 100 ml Vial Contains 200 mg Ciprofloxacin
Ciprofloxacin 2 mg/ml Infusion
100 ml
Each 100 ml Vial Contains 200 mg Ciprofloxacin
Claris

130 x 34 mm PANTONE 357 C
7 point font size Black



PANTONE 357 C
Black

130 x 65 mm
7 point Font size


PANTONE 357 C
Black
51 x 51 x 80 mm
Sterile, single dose container.
Each 50 ml contains :
Active Material :
Ciprofloxacin Lactate equivalent to
100 mg Ciprofloxacin.
Other Ingredients :
Lactic Acid
Sodium Chloride
Hydrochloric Acid
Water for Injections
Dosage : Use as directed by a Medical Practitioner.
Storage : Do not store above 25°C. Keep container in outer carton. Do not refrigerate or freeze.
Ciprofloxacin
2 mg/ml Infusion
50 ml
Each 50 ml Vial Contains
100 mg Ciprofloxacin
Claris
Ciprofloxacin 2 mg/ml Infusion
Each 50 ml Vial Contains
100 mg Ciprofloxacin
POM
1 x 50 ml
Keep out of the reach and sight of children.
For Intravenous (I.V.) use only.
M.A. No. PL 20568/0003
Batch :
Man. :
Exp. :
Caution : Do not use if container is found leaking or solution is not clear. Solutions containing visible solid particles must not be used. Discard any unused portion of the contents.
Marketing Authorisation Holder :
Claris Lifesciences UK Limited
Crewe Hall, Crewe, Cheshire,
CW1 6UL, United Kingdom.
Ciprofloxacin
2 mg/ml Infusion
50 ml
Each 50 ml Vial Contains
100 mg Ciprofloxacin
Ciprofloxacin
2 mg/ml Infusion
50 ml
Each 50 ml Vial Contains
100 mg Ciprofloxacin
Claris