Public Assessment Report

Ciprofloxacin 2mg/ml solution for infusion

Ciprofloxacin

PL 24780/0001

Villerton Invest SA

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Lay Summary

The MHRA granted Villerton Invest SA a Marketing Authorisation for the medicinal product Ciprofloxacin 2mg/ml solution for infusion on 07/01/2009. This is a prescription only medicine, indicated for the treatment of certain bacterial infections and is to be administered by a healthcare professional.

The originator product/UK reference product is Ciproxin infusion; Bayer PLC; PL 00010/0150. Ciprofloxacin 2mg/ml solution for infusion was demonstrated to be a generic medical product of the reference product.

Scientific Discussion

INTRODUCTION

The MHRA granted Villerton Invest SA a Marketing Authorisation for the medicinal product Ciprofloxacin 2mg/ml solution for infusion on 07/01/2009. This is a prescription only medicine and is indicated for the treatment of certain bacterial infections as listed in the Summary of Product Characteristics (page 8).

The originator product/UK reference product (Ciproxin infusion; Bayer PLC; PL 00010/0150) was first authorised in 1987. The Villerton application is considered valid. This is a National Standard Abridged Application for Ciprofloxacin 2mg/ml infusion made under article 10.1 of Directive 2001/83/EC.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

An appropriate specification based on the European Pharmacopoeia with the addition of a test for residual ethanol, has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Ciprofloxacin drug substance is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

DRUG PRODUCT

Other Ingredients

The other components of the drug product are lactic acid solution, glucose monohydrate and water for injection. Specifications and certificates of analysis have been provided for lactic acid solution, water for injection and glucose monohydrate as evidence of compliance with their respective Ph.Eur. monographs. The applicant states that no excipients of human or animal origin are used in the product.

Impurity profiles
The impurity profile for the drug product was found to be similar to that for the reference product.

Manufacture
A description and flow-chart of the manufacturing method have been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
The product is supplied in PVC infusion bags containing 50ml, 100ml and 200ml of infusion solution. The bags meet current Ph Eur requirements.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years has been set, with the following storage conditions “store in the original package” and “Do not refrigerate or freeze”.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY AND ADVICE

A Marketing Authorisation was granted.

PRECLINICAL ASSESSMENT

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

MEDICAL ASSESSMENT

Introduction

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.

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.

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.

Bioequivalence

As the product is an intravenous aqueous solution no bioequivalence study is required.

Clinical Efficacy

The applicant presents the results of a comprehensive bibliographic search. No new clinical trials were performed for this application and none are required.

Clinical Safety

No new signals were identified in the bibliographic search presented by the applicant. It should be noted that Section 4.4 of the SPC of the reference product was recently updated to include warnings regarding hypersensitivity and the administration of peristalsis inhibiting drugs, and to strengthen the warning on photosensitivity reactions.

Clinical Expert Report

A satisfactory clinical expert re[port was provided, written by a suitably qualified expert.

Summary of Product Characteristics, Patient Information Leaflet and Labelling

These were satisfactory.

Conclusion

A Market Authorisation may be granted.

Overall Conclusion and Risk/Benefit Analysis

Quality

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

Pre-Clinical

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

Clinical

No bioequivalence study was required for this intravenous product. A satisfactory expert report was provided.

No new or unexpected safety concerns arise from this application.

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

Risk/Benefit Analysis

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The risk/benefit is, therefore, considered positive.

Steps Taken During Assessment

1	The MHRA received the application on 17/10/2005
2	Following standard checks and communication with the applicant the MHRA considered the application valid on 15/11/2005.
3	Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 31/01/2006, 16/10/2006 and 22/07/2008 and on the medical assessment on 27/10/2006 and 10/07/2007.
4	The applicant provided further information in regard to the quality assessment on 02/05/2006, 22/01/2007 28/12/2007 and 01/10/2008 and on the medical assessment on 02/05/2006, 22/01/2007 and 01/10/2008.
5	The application was determined on 07/01/2009.

Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2mg/ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bag contains 2 mg/ml ciprofloxacin (as lactate).
The 50 ml bag contain 100 mg ciprofloxacin (as lactate)
The 100 ml bag contains 200 mg ciprofloxacin (as lactate)
The 200 ml bag contains 400 mg ciprofloxacin (as lactate)

Excipients:
Glucose (see section 4.4).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless solution

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ciprofloxacin 2mg/ml solution for infusion is indicated for the treatment of the following infections (see sections 4.4 and 5.1). Special attention should be paid to available information on resistance to ciprofloxacin before commencing therapy.

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

Adults

- Lower respiratory tract infections due to Gram-negative bacteria

- exacerbations of chronic obstructive pulmonary disease
- broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- pneumonia

- Chronic suppurative otitis media

- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria
- Urinary tract infections
- Epididymo-orchitis including cases due to *Neisseria gonorrhoeae*
- Pelvic inflammatory disease including cases due to *Neisseria gonorrhoeae*

  In the above genital tract infections when thought or known to be due to *Neisseria gonorrhoeae* it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.
- Infections of the gastro-intestinal tract (e.g. travellers` diarrhoea)
- Intra-abdominal infections
- Infections of the skin and soft tissue caused by Gram-negative bacteria
- Malignant external otitis
- Infections of the bones and joints
- Treatment of infections in neutropenic patients
- Prophylaxis of infections in neutropenic patients
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Children and adolescents

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

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

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

4.2 Posology and method of administration

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

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

After intravenous initiation of treatment, the treatment can be switched to oral treatment with tablet or suspension if clinically indicated at the discretion of

the physician. IV treatment should be followed by oral route as soon as possible.

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

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

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

Adults

Indications		**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory tract		400 mg twice daily to 400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Chronic suppurative otitis media	400 mg twice daily to 400 mg three times a day	7 to 14 days
	Malignant external otitis	400 mg three times a day	28 days up to 3 months
Urinary tract infections	Complicated and uncomplicated pyelonephritis	400 mg twice daily to 400 mg three times a day	7 to 21 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses)
	Prostatitis	400 mg twice daily to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days

Indications		Daily dose in mg	Total duration of treatment (including switch to oral therapy as soon as possible)
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	400 mg twice daily	1 day
	Diarrhoea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholerae*	400 mg twice daily	3 days
	Typhoid fever	400 mg twice daily	7 days
	Intra-abdominal infections due to Gram-negative bacteria	400 mg twice daily to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice daily to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice daily to 400 mg three times a day	max. of 3 months
Treatment of infections or prophylaxis of infections in neutropenic patients Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice daily to 400 mg three times a day	Therapy should be continued over the entire period of neutropenia
Inhalation anthrax post-exposure prophylaxis and curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.		400 mg twice daily	60 days from the confirmation of *Bacillus anthracis* exposure

Children and adolescents

Indication	**Daily dose in mg**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Cystic fibrosis	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	10 to 21 days
Inhalation anthrax post-exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 400 mg per dose.	60 days from the confirmation of *Bacillus anthracis* exposure
Other severe infections	10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	According to the type of infections

Geriatric patients

Geriatric patients should receive a dose selected according to the severity of the infection and the patient`s creatinine clearance.

Renal and hepatic impairment

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [mL/min/1.73 m²]	**Serum Creatinine [µmol/L]**	**Intravenous Dose [mg]**
> 60	< 124	See Usual Dosage.
30-60	124 to 168	200-400 mg every 12 h
< 30	> 169	200-400 mg every 24 h

Patients on haemodialysis	> 169	200-400 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	200-400 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

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

Method of administration

Ciprofloxacin 2mg/ml solution for infusion should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion. For children, the infusion duration is 60 minutes.
In adult patients, infusion time is 60 minutes for 400 mg of Ciprofloxacin 2mg/ml solution for infusion and 30 minutes for 200 mg of Ciprofloxacin 2mg/ml solution for infusion. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.
The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (see section 6.2).

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4 Special warnings and precautions for use

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

Streptococcal Infections (including Streptococcus pneumoniae)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Genital tract infections
Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-

resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on in-vitro susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Children and adolescents
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

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

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

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify a ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

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

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, as soon as the first 48 hours of treatment. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8).
At any sign of tendinitis (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.
Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

Central Nervous System
Quinolones are known to trigger seizures or lower the seizure threshold. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-endangering behaviour. In these cases, ciprofloxacin should be discontinued.
Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin. Ciprofloxacin should

be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

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

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

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

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phosphate dehydrogenase deficiency
Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be

monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

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

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

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

Glucose Load
Ciprofloxacin 2mg/ml solution for infusion contains 5.5 g glucose in 100 ml solution for infusion. This should be taken into account in patients with diabetes mellitus.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products on ciprofloxacin:

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

Effects of ciprofloxacin on other medicinal products:

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

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

Theophylline

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

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

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

Oral anticoagulants
Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects. There have been many reports of increases in oral anti-coagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

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

Clozapine
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

4.6 Pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature

organism / foetus (see section 5.3). As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

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

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome) (see section 4.4)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Immune System Disorders			Allergic reaction Allergic oedema / angio-oedema	Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression Hallucinations	Psychotic reactions (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (see section 4.4) Vertigo	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension	Peripheral neuropathy (see section 4.4)
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, QT prolongation, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4)	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1 000	Very Rare < 1/10 000	**Frequency not known** (cannot be estimated from available data)
Musculoskeletal, Connective Tissue and Bone Disorders		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions	Injection and infusion site reactions (only intravenous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

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

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

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

Paediatric patients

The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

4.9 Overdose

An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure. Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

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

PK/PD relationship:
Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of

ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

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

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

Spectrum of antibacterial activity:
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

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

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

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

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

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

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

Aerobic Gram-negative micro-organisms *Acinetobacter baumannii*[+] *Burkholderia cepacia* [+]* *Campylobacter* spp.[+]* *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae* * *Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumoniae** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis** *Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobic micro-organisms *Peptostreptococcus* spp. *Propionibacterium acnes*
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms *Actinomyces* *Enteroccus faecium* *Listeria monocytogenes*
Aerobic Gram-negative micro-organisms *Stenotrophomonas maltophilia*
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms *Mycoplasma genitalium* *Ureaplasma urealitycum*
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications [+] Resistance rate ≥ 50% in one or more EU countries ($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance (1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and /or international consensus documents regarding treatment of anthrax. (2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50%

among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption

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

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

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

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

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

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

Distribution

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

Metabolism

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

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

Elimination

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

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

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

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

Paediatric patients
The pharmacokinetic data in paediatric patients are limited.

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

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

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.
Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/ photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactic acid solution
Glucose monohydrate
Water for Injection

6.2 Incompatibilities

Ciprofloxacin infusion should not be mixed with injection solutions (e.g. penicillins, heparin solutions) which are chemically or physically unstable at its pH of 3.5 – 4.6. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products and should always be administered separately.

6.3 Shelf life

Two years.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Store in the original package.

6.5 Nature and contents of container

50ml, 100ml or 200ml PVC bag contained in a polypropylene/polyester-aluminium/polyester pouch. Pack sizes of 10 bags

6.6 Special precautions for disposal

Since the infusion solution is photosensitive, the infusion bags should be removed from the box only immediately before use. In daylight conditions complete efficacy is guaranteed for a period of three days.

Any unused solution should be disposed off.

7 MARKETING AUTHORISATION HOLDER

Villerton Invest SA
8-10 Rue Jean Monnet
L-2180 Luxembourg

8 MARKETING AUTHORISATION NUMBER(S)

PL 24780/0001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/01/2009

10 DATE OF REVISION OF THE TEXT

Labels and Leaflets

(Ciprofloxacin 100mg/50ml, 200mg/100ml and 400mg/200ml)

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

In this leaflet:
1. What Ciprofloxacin Infusion is and what it is used for
2. Before you are given Ciprofloxacin Infusion
3. How to use Ciprofloxacin Infusion
4. Possible side effects
5. How to store Ciprofloxacin Infusion
6. Further information

1. WHAT CIPROFLOXACIN INFUSION IS AND WHAT IT IS USED FOR

Ciprofloxacin Infusion is an antibiotic belonging to the fluoroquinolone family. The active substance is ciprofloxacin. Ciprofloxacin works by killing bacteria that cause infections. It only works with specific strains of bacteria.

Adults

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

If you have a severe infection or one that is caused by more than one type of bacterium, you may be given additional antibiotic treatment in addition to Ciprofloxacin Infusion.

Children and adolescents

Ciprofloxacin Infusion is used in children and adolescents, under specialist medical supervision, to treat the following bacterial infections:
- lung and bronchial infections in children and adolescents suffering from cystic fibrosis
- complicated urinary tract infections, including infections that have reached the kidneys (pyelonephritis)
- anthrax inhalation exposure

Ciprofloxacin Infusion may also be used to treat other specific severe infections in children and adolescents when your doctor considers this necessary.

2. BEFORE YOU ARE GIVEN CIPROFLOXACIN INFUSION

You must not be given Ciprofloxacin Infusion if you are:
- allergic (hypersensitive) to the active substance, to other quinolone drugs or to any of the other ingredients of Ciprofloxacin Infusion (see section 6)
- taking tizanidine (See Section 2: Taking other medicines)

Take special care with Ciprofloxacin Infusion
Before you are given Ciprofloxacin Infusion, tell your doctor if you:
- have ever had kidney problems because your treatment may need to be adjusted
- suffer from epilepsy or other neurological conditions
- have a history of tendon problems during previous treatment with antibiotics such as Ciprofloxacin Infusion
- have myasthenia gravis (a type of muscle weakness)
- have a history of abnormal heart rhythms (arrythmias)

While under treatment with Ciprofloxacin Infusion

Tell your doctor immediately if any of the following occurs **during treatment with Ciprofloxacin Infusion.** Your doctor will decide whether treatment with Ciprofloxacin Infusion needs to be stopped.

- **Severe, sudden allergic reaction** (an anaphylactic reaction/shock, angio-oedema). Even with the first dose, there is a rare chance that you may experience a severe allergic reaction with the following symptoms: tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing. **If this happens, tell your doctor immediately since the administration of Ciprofloxacin Infusion will have to be stopped.**
- **Pain and swelling in the joints, and tendinitis** may occur occasionally particularly if you are elderly and are also being treated with corticosteroids. At the first sign of any pain or inflammation Ciprofloxacin Infusion will have to be stopped. Rest the painful area. Avoid any unnecessary exercise as this might increase the risk of a tendon rupture.
- If you suffer from **epilepsy** or other **neurological conditions** such as cerebral ischemia or stroke, you may experience side effects associated with the central nervous system. If this happens, stop taking Ciprofloxacin Infusion and contact your doctor immediately.
- You may experience **psychiatric reactions** after first administration of ciprofloxacin. If you suffer from **depression** or psychosis, your symptoms may become worse under treatment with Ciprofloxacin Infusion. If this happens, stop taking Ciprofloxacin Infusion and contact your doctor immediately.
- You may experience symptoms of neuropathy such as pain, burning, tingling, numbness and/or weakness. If this happens, stop taking Ciprofloxacin Infusion and contact your doctor immediately.
- **Diarrhoea** may develop while you are on antibiotics, including Ciprofloxacin Infusion or even several weeks after you have stopped using them. If it becomes severe or persistent or you notice that your stool contains blood or mucus, tell your doctor immediately. Ciprofloxacin Infusion treatment will have to be stopped immediately, as this can be life-threatening. Do not take medicines that stop or slow down bowel movements.
- Tell the doctor or laboratory staff that you are taking Ciprofloxacin Infusion if you have to provide a **blood or urine sample.**
- Ciprofloxacin Infusion may cause **liver damage.** If you notice any symptoms such as loss of appetite, jaundice (yellowing of the skin), dark urine, itching, or tenderness of the stomach, Ciprofloxacin Infusion must be stopped immediately.
- Ciprofloxacin Infusion may cause a reduction in the number of white blood cells and your **resistance to infection may be decreased.** If you experience an infection with symptoms such as fever and serious deterioration of your general condition, or fever with local infection symptoms such as sore throat/pharynx/mouth or urinary problems you should see your doctor immediately. A blood test will be taken to check possible reduction of white blood cells (agranulocytosis). It is important to inform your doctor about your medicine.
- Tell your doctor if you or a member of your family is known to have a deficiency in glucose-6-phosphate dehydrogenase (G6PD), since you may experience a risk of anaemia with ciprofloxacin.
- Your skin becomes more **sensitive to sunlight or ultraviolet (UV) light** under treatment with Ciprofloxacin Infusion. Avoid exposure to strong sunlight or artificial UV light such as sunbeds.

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

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

The following medicines are known to interact with Ciprofloxacin Infusion in your body. Using Ciprofloxacin Infusion together with these medicines can influence the therapeutic effect of these medicines. It can also increase the probability of experiencing side effects.

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

Ciprofloxacin Infusion may increase the levels of the following medicines in your blood:
- pentoxifylline (for circulatory disorders)
- caffeine

Taking Ciprofloxacin Infusion with food and drink
Food and drink does not affect your treatment with Ciprofloxacin Infusion.

Pregnancy and breast-feeding
It is preferable to avoid the use of Ciprofloxacin Infusion during pregnancy. Tell your doctor if you are planning to get pregnant.

Do not take Ciprofloxacin Infusion during breast feeding because ciprofloxacin is excreted in breast milk and can be harmful for your child.

Driving and using machines
Ciprofloxacin Infusion may make you feel less alert. Some neurological adverse events can occur. Therefore, make sure you know how you react to Ciprofloxacin Infusion before driving a vehicle or operating machinery. If in doubt, talk to your doctor.

Important information about some of the ingredients of Ciprofloxacin Infusion
This medicine contains 5.5g glucose per 100ml of infusion solution. This should be taken into account in patients with diabetes mellitus.

The following information is intended for medical or healthcare professionals only

Ciprofloxacin infusion should be administered by intravenous infusion. For children, the infusion duration is 60 minutes. In adult patients, the infusion time is 60 minutes for 400 mg Ciprofloxacin infusion and 30 minutes for 200 mg Ciprofloxacin infusion. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions.

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

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

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

FRONT

3. HOW TO USE CIPROFLOXACIN INFUSION

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

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

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

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

Remember to drink plenty of fluids while you are taking Ciprofloxacin infusion.

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

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Ciprofloxacin infusion can cause side effects, although not everybody gets them.

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

Common side effects (between 1 and 10 in every 100 people are likely to get these):
- nausea, diarrhoea, vomiting
- joint pains in children
- local reaction at the injection site, rash
- temporary increased amounts of substances in the blood (transaminases)

Uncommon side effects (between 1 and 10 in every 1,000 people are likely to get these):
- fungal superinfections
- a high concentration of eosinophils, a type of white blood cell, increased or decreased amounts of a blood clotting factor (thrombocytes)
- loss of appetite (anorexia)
- hyperactivity, agitation, confusion, disorientation, hallucinations
- headache, dizziness, sleeping problems, taste disorders, pins and needles, unusual sensitivity to stimuli of the senses, seizures (see Section 2: Take special care with Ciprofloxacin infusion), giddiness
- eyesight problems
- loss of hearing
- rapid heartbeat (tachycardia)
- expansion of the blood vessels (vasodilation), low blood pressure
- abdominal pain, digestive problems such as stomach upset (indigestion/heartburn), wind
- liver disorders, increased amounts of one substance in the blood (bilirubin), jaundice (cholestatic icterus)
- itching, hives
- joint pain in adults
- poor kidney function, kidney failure
- pains in your muscles and bones, feeling unwell (asthenia), fever, fluid retention
- increase in blood alkaline phosphatase (a certain substance in the blood)

Rare side effects (between 1 and 10 in every 10,000 people are likely to get these):
- inflammation of the bowel (colitis) linked to antibiotic use (can be fatal in rare cases) (see Section 2: Take special care with Ciprofloxacin infusion)
- changes to the blood count (leukopenia, leukocytosis, neutropenia, anaemia), a drop in the number of red and white blood cells and platelets (pancytopenia), which may be fatal, bone-marrow depression which may also be fatal (see Section 2: Take special care with Ciprofloxacin infusion)
- allergic reaction, allergic swelling (oedema), rapid swelling of the skin and mucous membranes (angioedema), severe allergic reaction (anaphylactic shock) which can be life-threatening (see Section 2: Take special care with Ciprofloxacin infusion
- increased blood sugar (hyperglycaemia)
- anxiety reaction, strange dreams, depression, mental disturbances (psychotic reactions) (see Section 2: Take special care with Ciprofloxacin infusion
- decreased skin sensitivity, tremor, migraine, disorder of sense of smell (olfactory disorders)
- tinnitus, impaired hearing
- fainting, inflammation of the blood vessel (vasculitis)
- shortness of breath including asthmatic symptoms
- pancreatitis
- hepatitis, death of liver cells (liver necrosis) very rarely leading to life-threatening liver failure
- sensitivity to light (see Section 2: Take special care with Ciprofloxacin infusion), small, pin-point bleeding under the skin (petechiae)
- muscle pain, inflammation of the joints, increased muscle tone, cramping, tendon rupture – especially of the large tendon at the back of the ankle (Achilles' tendon) (see Section 2: Take special care with Ciprofloxacin infusion)
- blood or crystals in the urine (see Section 2: Take special care with Ciprofloxacin infusion), Urinary tract inflammation
- excessive sweating
- abnormal levels of a clotting factor (prothrombin) increased levels of the enzyme amylase

Very rare side effects (less than 1 in every 10,000 people are likely to get these):
- a special type of reduced red blood cell count (haemolytic anaemia); a dangerous drop in a type of white blood cells (agranulocytosis)
- severe allergic reaction (anaphylactic reaction, anaphylactic shock, serum sickness) which can be fatal (see Section 2: Take special care with Ciprofloxacin infusion)
- disturbed coordination, unsteady walk (gait disturbance), pressure on the brain (intracranial pressure)
- visual colour distortions
- various skin eruptions or rashes (e.g. the potentially fatal Stevens-Johnson syndrome or toxic epidermal necrolysis)
- muscle weakness, tendon inflammation, worsening of the symptoms of myasthenia gravis (see Section 2: Take special care with Ciprofloxacin infusion)

Frequency not known (cannot be estimated from the available data)
- troubles associated with the nervous system such as pain, burning, tingling, numbness and/ or weakness in extremities
- severe cardiac rhythm abnormalities, irregular heart beat (Torsades de Pointes)

5. HOW TO STORE CIPROFLOXACIN INFUSION

Store in the original package. Do not refrigerate or freeze.

Keep out of the reach and sight of children.

Do not use Ciprofloxacin infusion after the expiry date which is stated on the carton after 'EXP'. The expiry date refers to the last day of that month.

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

6. FURTHER INFORMATION

What Ciprofloxacin infusion contains
The active ingredient is ciprofloxacin (as ciprofloxacin lactate).
The other ingredients are lactic acid solution, glucose monohydrate and water for injection.

What Ciprofloxacin infusion looks like and contents of the pack
Solution for infusion.
Ciprofloxacin infusion is available in 50ml, 100ml or 200ml PVC bags. The 50ml bag contains 100mg Ciprofloxacin, the 100ml bag contains 200mg Ciprofloxacin and the 200ml bag contains 400mg Ciprofloxacin.

Marketing Authorisation Holder
Villerton Invest SA, 8-10 Rue Jean Monnet, L-2180 Luxembourg

Manufacturer
ACS Dobfar INFO SA, CH-7748 Campascio, Switzerland.

This leaflet was last approved in (MM/YYYY)

Advice/medical education

Antibiotics are used to cure bacterial infections. They are ineffective against viral infections.
If your doctor has prescribed antibiotics, you need them precisely for your current illness. Despite antibiotics, some bacteria may survive or grow. This phenomenon is called resistance: some antibiotic treatments become ineffective.
Misuse of antibiotics increases resistance. You may even help bacteria become resistant and therefore delay your cure or decrease antibiotic efficacy if you do not respect appropriate:
- dosage
- schedules
- duration of treatment

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

L08347802


Ciprofloxacin 2mg/ml
Solution for Infusion
400mg / 200ml
in 5% w/v dextrose
1 single sterile unit PVC bag.
Contains 400mg ciprofloxacin (as lactate) in 200 ml. Also contains 5% w/v dextrose, 0.06% w/v lactic acid and water for injection.
For intravenous infusion over 30-60 minutes. For single use as directed by the physician. Please read package insert before use. Do not remove from outer foil until ready for use and use promptly when outer is opened. Do not refrigerate or freeze. Store in the original container. Do not mix or co-administer with other products or infusion solutions. Must not be used in series connections. Use only if solution is clear. Check for minute leaks prior to use as, if found, sterility cannot be guaranteed. Discard any unused portion immediately after use. Keep out of the reach and sight of children.
PL 24780/0001
Villerton Invest SA
8-10, Rue Jean Monnet, L-2180 Luxembourg
Distributed by Bowmed Ibisqus Limited
Cheltenham, GL50 1NW UK
POM
5 060130 130287
O08CFX200
Ciprofloxacin 400mg / 200ml
Batch:
Exp.Date:

Ciprofloxacin 2mg/ml

Solution for Infusion

400mg / 200ml

in 5% w/v dextrose

Ciprofloxacin (as lactate) 400 mg in 200 ml, 0.06% w/v lactic acid, 5% w/v dextrose, water for injection.

For I.V. infusion over 30 - 60 minutes. Store in the original container. Do not refrigerate or freeze. Keep out of the reach and sight of children. For single use only.
Please read package insert before use.

PL 24780/0001
EAN 5 060130 130287

POM

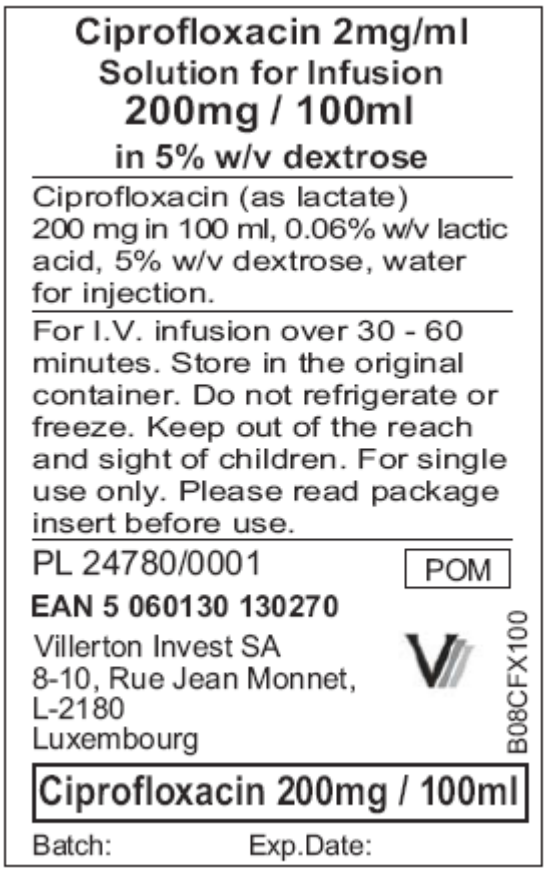
Villerton Invest SA
8-10, Rue Jean Monnet,
L-2180
Luxembourg

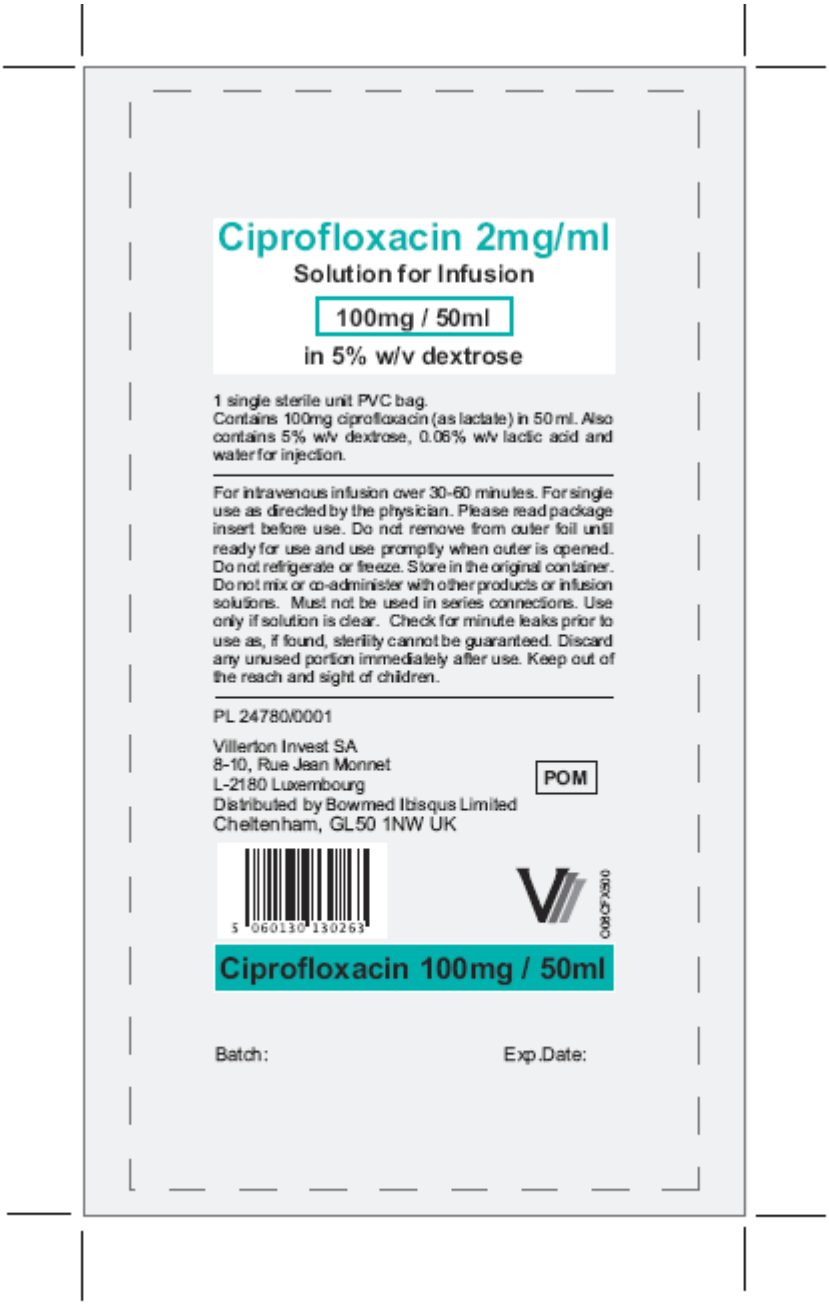
B08CFX200

Ciprofloxacin 400mg / 200ml

Batch: Exp.Date:


Ciprofloxacin 2mg/ml
Solution for Infusion
200mg / 100ml
in 5% w/v dextrose
1 single sterile unit PVC bag.
Contains 200mg ciprofloxacin (as lactate) in 100 ml. Also contains 5% w/v dextrose, 0.06% w/v lactic acid and water for injection.
For intravenous infusion over 30-60 minutes. For single use as directed by the physician. Please read package insert before use. Do not remove from outer foil until ready for use and use promptly when outer is opened. Do not refrigerate or freeze. Store in the original container. Do not mix or co-administer with other products or infusion solutions. Must not be used in series connections. Use only if solution is clear. Check for minute leaks prior to use as, if found, sterility cannot be guaranteed. Discard any unused portion immediately after use. Keep out of the reach and sight of children.
PL 24780/0001
Villerton Invest SA
8-10, Rue Jean Monnet
L-2180 Luxembourg
Distributed by Bowmed Ibisqus Limited
Cheltenham, GL50 1NW UK
POM
5 060130 130270
CIPROFX100
Ciprofloxacin 200mg / 100ml
Batch:
Exp.Date:


Ciprofloxacin 2mg/ml
Solution for Infusion
200mg / 100ml
in 5% w/v dextrose
Ciprofloxacin (as lactate)
200 mg in 100 ml, 0.06% w/v lactic acid, 5% w/v dextrose, water for injection.
For I.V. infusion over 30 - 60 minutes. Store in the original container. Do not refrigerate or freeze. Keep out of the reach and sight of children. For single use only. Please read package insert before use.
PL 24780/0001
POM
EAN 5 060130 130270
Villerton Invest SA
8-10, Rue Jean Monnet,
L-2180
Luxembourg
B08CFX100
Ciprofloxacin 200mg / 100ml
Batch:
Exp.Date:


Ciprofloxacin 2mg/ml
Solution for Infusion
100mg / 50ml
in 5% w/v dextrose
1 single sterile unit PVC bag.
Contains 100mg ciprofloxacin (as lactate) in 50 ml. Also contains 5% w/v dextrose, 0.06% w/v lactic acid and water for injection.
For intravenous infusion over 30-60 minutes. For single use as directed by the physician. Please read package insert before use. Do not remove from outer foil until ready for use and use promptly when outer is opened. Do not refrigerate or freeze. Store in the original container. Do not mix or co-administer with other products or infusion solutions. Must not be used in series connections. Use only if solution is clear. Check for minute leaks prior to use as, if found, sterility cannot be guaranteed. Discard any unused portion immediately after use. Keep out of the reach and sight of children.
PL 24780/0001
Villerton Invest SA
8-10, Rue Jean Monnet
L-2180 Luxembourg
Distributed by Bowmed Ibisqus Limited
Cheltenham, GL50 1NW UK
POM
5 060130 130263
Ciprofloxacin 100mg / 50ml
Batch:
Exp.Date:


Ciprofloxacin 2mg/ml
Solution for Infusion
100mg / 50ml
in 5% w/v dextrose
Ciprofloxacin (as lactate)
100 mg in 50 ml, 0.06% w/v lactic acid, 5% w/v dextrose, water for injection.
For I.V. infusion over 30 - 60 minutes. Store in the original container. Do not refrigerate or freeze. Keep out of the reach and sight of children. For single use only. Please read package insert before use.
PL 24780/0001
POM
EAN 5 060130 130263
Villerton Invest SA
8-10, Rue Jean Monnet,
L-2180
Luxembourg
B08CFX500
Ciprofloxacin 100mg / 50ml
Batch:
Exp.Date: