Public Assessment Report

Mutual Recognition Procedure

Ciprofloxacin 2mg/ml Solution for Infusion

Ciprofloxacin

UK/H/1092/01/MR

UK Licence no: PL 24598/0009

Noridem Enterprises Limited

LAY SUMMARY

Austria, Germany, Ireland, Spain and Greece approved Noridem Enterprises Limited a Marketing Authorisation (licence) for the medicinal product Ciprofloxacin 2mg/ml Solution for Infusion. This is a prescription-only medicine (POM) that is used to treat infections caused by bacteria (germs).

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

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

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Module 1

Product Name	Ciprofloxacin 2mg/ml Solution For Infusion
Type of Application	Generic, Article 10.1
Active Substance	ciprofloxacin
Form	Solution for Intravenous Infusion
Strength	2mg/ml
MA Holder	Noridem Enterprises Ltd, Evagorou and Makariou, Mitsi Building 3, Suite 115, 1065 Nicosia, Cyprus
RMS	UK
CMS	Austria, Germany, Ireland, Spain and Greece
Procedure Number	UK/H/1092/01/MR
Timetable	Day 90: 4th December 2007

Module 2

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 2 mg/ml Solution for Infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For full list of excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- the respiratory tract. Ciprofloxacin may be indicated for treating pneumonia due to gram-negative pathogens. Ciprofloxacin is not the drug of choice for the treatment of pneumococcal pneumonia
- the ear and the sinuses, especially when gram-negative bacteria are implicated
- the urinary tract, such as complicated infections and pyelonephritis
- the genital organs, including gonorrhoea and prostatitis
- the pelvic organs, such as salpingitis, endometritis and pelvic inflammatory disease
- intra-abdominal organs, including peritonitis and biliary tract infections
- enteric (typhoid) fever
- the skin and soft tissue
- the bones and joints
- severe systemic infections: septicaemia, infections in immunosuppressed patients

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

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

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

4.2 Posology and Method of Administration

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

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

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

The following dosages are recommended for specific types of infections:

Table 1: Recommended Adult Dosage

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

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

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

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

Impaired Hepatic Function
No adjustment of dosage is necessary

Duration
The duration of treatment depends upon the severity of the disorder and on the clinical and bacteriological course. Treatment that has been initiated with intravenous injection may be switched to oral therapy according to the condition of the patient.
Acute infections: the usual total treatment period is 5 - 7 days.

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

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

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

4.3 Contraindications

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

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

4.4 Special warnings and precautions for use

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

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

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

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

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

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

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

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

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

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

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

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

Xanthine derivative

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

NSAIDs

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

Cyclosporin

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

Anticoagulants

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

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

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

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

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

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

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

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

In a crossover study, 10 healthy subjects were given ciprofloxacin 500mg or placebo twice daily for three days, at the end of which a single dose of tizanidine 4mg was given. There was an increase in tizanidine serum concentrations (Cmax increase: 7-fold, range: 4 to 21 fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin compared to placebo. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (refer to Section 4.3)

4.6 Pregnancy and Lactation

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

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

4.7. Effects on ability to drive and use machinery

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

4.8. Undesirable effects

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

The following undesirable effects have been observed:

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

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

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

Hypersensitivity reactions
The following reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, Ciprofloxacin is to be discontinued immediately and the treating physician informed.
Common (>1/100, <1/10): skin reactions such as rash, pruritus, drug fever.
Very rare (< 1/10,000):

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

Effects on the cardiovascular system
Uncommon (> 1/1,000, <1/100): palpitation
Very rare (< 1/10,000): peripheral oedema, hot flushes, migraine, fainting, tachycardia.

Effects on the locomotor apparatus
Uncommon (> 1/1,000, <1/100): arthralgia and joint swelling
Very rare (< 1/10,000): muscle pains, inflammation of the tendon sheaths (tenosynovitis).

In isolated cases: tendonitis and torn tendons (eg of Achilles' tendon) may occur during treatment with fluoroquinolones. These events were observed predominantly among older patients who had been systematically treated beforehand with corticosteroids. If tendonitis is suspected, treatment with Ciprofloxacin must be discontinued immediately, physical effort avoided and, if necessary, medical treatment initiated. Aggravation of the sympthoms of myasthenia gravis.

Effects on the blood and blood components
Uncommon (> 1/1,000, <1/100): eosinophilia, leucopenia, granulocytopenia, anaemia, thrombocytopenia.

Very rare (<1/10,000): leucocytosis, thrombocytosis, haemolytic anaemia, pancytopneia, agranulocytosis, altered prothrombin values.

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

In isolated cases: hyperglycaemia, crystalluria or haematuria.

Others
Uncommon (> 1/1,000, <1/100): pulmonary embolism, dyspnoea, pulmonary oedema, epistaxis, hemoptysis and hiccough.

Very rare (< 1/10,000): asthenia, a transient impairment of kidney function to transient renal failure.

Photosensitivity: it is recommended that patients avoid long lasting exposure to sunlight or irradiation with UV-light (solarium) during treatment with ciprofloxacin; treatment should be discontinued in cases of photosensitivity reactions (eg skin reactions similar to sun burn).

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

4.9. Overdose

Based on the limited information available in two cases of ingestion of over 18g of ciprofloxacin, reversible renal toxicity has occurred. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients must be kept well hydrated and, in the case of renal damage resulting in prolonged oliguria, dialysis should be initiated.

Serum levels of ciprofloxacin are reduced by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones
ATC Code: J01 MA 02

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

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

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

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

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

Anaerobes
Peptococcus spp.
Peptostreptococcus spp.
Veillonella parvula

Other pathogens
Legionella pheumophila

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

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

Other pathogens
Chlamydia spp.[+]

Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.

Gram-negative aerobes
Stenotrophomonas maltophila

Anaerobes
Bacteroides fragilis group

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

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

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

5.2. Pharmacokinetic properties

Absorption:
After oral administration, ciprofloxacin is predominantly absorbed from the deuodenum and upper jejunum and reaches peak serum concentrations within 60-90 min. After single doses of 250mg and 500mg C_{max} values are about 0.8-2.0 mg/l and 1.5-2.9 mg/l respectively.

The absolute bioavailability is approximately 70 to 80%. C_{max}– and AUC- values are proportionally increased with the dose.

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

Metabolism/Elimination
Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5 ml/min/kg, and total clearance amounts to 8-10 ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.

Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). M1 to M3 show antibacterial activity comparable with or smaller than nalidixic acid. M4 with the lowest quantity has an antimicrobial activity very much corresponding to norfloxacin.

Up to 70% of a parenteral dose may be excreted unchanged in urine within 24 hours and 10% as metabolites. Faecal excretion over 5 days has accounted for 15% of an intravenous dose.

Only small amounts of ciprofloxacin are removed by haemodialysis or peritoneal dialysis.

The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral and after intravenous administration.

Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renal function must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

Paediatrics
The pharmacokinetics of ciprofloxacin in children with cystic fibrosis differs from that in children without cystic fibrosis, and dosing recommendations are only applicable for children with cystic fibrosis.

Intravenous administration of 10mg/kg three times daily or oral administration of 20mg/kg twice daily to children with cystic fibrosis gives an exposure that is comparable to that in adults following an oral dose of 750mg twice daily.

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

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

6. PHARMACEUTICAL PARTICULARS

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

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

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

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

6.3. Shelf life
Unopened polypropylene bag:
Two years.

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

6.4 Special precautions for storage
Unopened polypropylene bag:

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

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

Do not refrigerate or freeze Ciprofloxacin 2 mg/ml Solution for Infusion. If the product is inadvertently refrigerated, crystals may form. Do not use if crystals are present. These crystals will, however, redissolve at room temperature and do not adversely affect the quality of the product.

6.5 Nature and contents of container

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

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

6.6 Instructions for use and handling

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

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

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

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

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

7. MARKETING AUTHORISATION HOLDER

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1065 Nicosia, Cyprus.

8. MARKETING AUTHORISATION NUMBERS

PL 24598/0009

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/10/2006

10 DATE OF REVISION OF THE TEXT

26/01/2007

Module 3
Patient Information Leaflet

Ciprofloxacin 2 mg/ml Solution for Infusion

Ciprofloxacin

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

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

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

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

In this leaflet:

1. What Ciprofloxacin is and what it is used for

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

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

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

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

2. Before you take Ciprofloxacin

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

Do not take Ciprofloxacin

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

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

Take special care with Ciprofloxacin

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

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

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

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

Please read the next page of this leaflet

Taking other medicines

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

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

- Anticoagulant drugs such as warfarin for making the blood thinner (may make the anticoagulant drug work more)
- Cyclosporin (may affect your kidneys for a short time).
- Glibenclamide (may make your blood sugar levels drop too low)
- Mexiletine (may make the amount of mexiletine in your blood too high)
- Non-steroidal anti-inflammatory drugs also called NSAIDs (may cause fits or seizures). You may take Aspirin.
- Phenytoin (may make the amount of phenytoin in your blood too high).

- Premedicants (medicines you get before an operation) such as papaveretum, atropine, hyoscine, diazepam and midazolam (may make the amount of Ciprofloxacin in your blood too low)
- Probenecid (may make the amount of Ciprofloxacin in your blood too high).
- Ropinirole (may give you more side effects)
- Theophylline, caffeine or pentoxyfilline (may give you more side effects)
- Tinazidine (your doctor will not give you Ciprofloxacin with this medicine as you may get more side effects such as low blood pressure and become very sleepy)
- Other medicines such as clozapine, tacrine (may make the amount of these medicines in your blood too high).

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

Pregnancy and breastfeeding

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

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

Driving and using machines

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

Important information about some of the ingredients of Ciprofloxacin

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

3. How to take Ciprofloxacin

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

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

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

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

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

Adults and elderly (over 65 years old):

The usual dose is 100 to 400 milligram (mg) twice daily (two times during the day) as an intravenous infusion (drip).

Doses for other infections are:

- Gonorrhoea: 100 mg as a single dose (one dose only)

- Urinary tract infections: 100 mg twice daily
- Adult patients with cystic fibrosis who get lung infections: 400 mg twice daily
- Other adult infections: 200 to 400 mg twice daily.

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

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

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

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

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

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

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

Please read the next page of this leaflet

4. Possible side-effects

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

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

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

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

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

The following are very rare side effects. They probably affect up to 1 in 10 000 people:
- small red spots on your skin which bleed, large blisters filled with blood, severe rash, sores and ulcers on your skin which may become serious and even life-threatening

- Problems with your kidneys and liver which may get worse and may be life-threatening
- Severe allergic reactions can sometimes happen with the first dose of Ciprofloxacin and can cause swelling of your face, throat and veins. This can lead to painful breathing and difficulty with breathing. You may go into shock and your reaction may be life-threatening. **Your doctor or nurse will also give you medical treatment for shock.**

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

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

Other possible side effects:
The following are common side effects probably affecting up to 1 in 10 people taking this medicine:
- nausea (feeling sick), diarrhoea, vomiting, stomach problems, pain in your belly, wind, loss of appetite
- dizziness, headache, tiredness, agitation, tremor (your limbs may shake), confusion

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

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

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

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

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

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

Please read the next page of this leaflet

5. How to store Ciprofloxacin

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

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

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

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

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

Open it and use it straight away.

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

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

6. Further information

What Ciprofloxacin contains

The active medicine is Ciprofloxacin lactate.
Each 50 ml (millilitre) bag will contain 100 mg (milligram) of ciprofloxacin. Each 100 ml (millilitre) bag will contain 200 mg (milligram) of ciprofloxacin. Each 200 ml bag will contain 400 mg of ciprofloxacin.

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

What Ciprofloxacin looks like and contents of the pack

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

Each bag of Ciprofloxacin contains 50ml, 100 ml or 200 ml of your medicine.
50ml and 100 ml bags come in boxes of 10.
200ml bags come in boxes of 5.

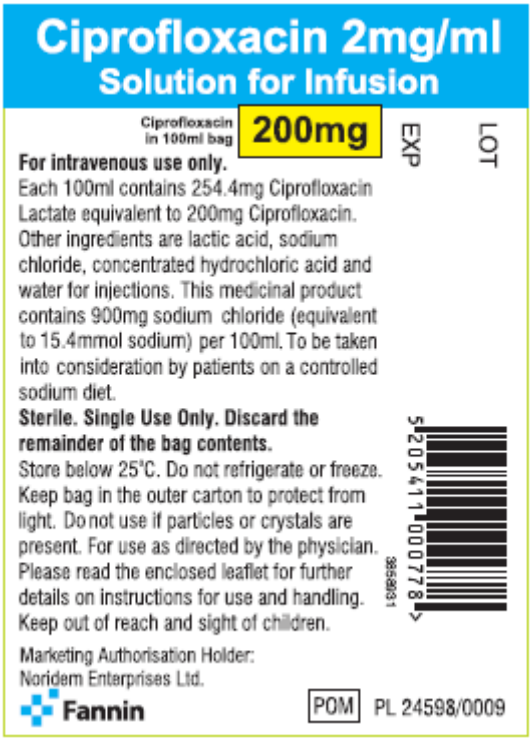
Marketing Authorisation Holder and Manufacturer

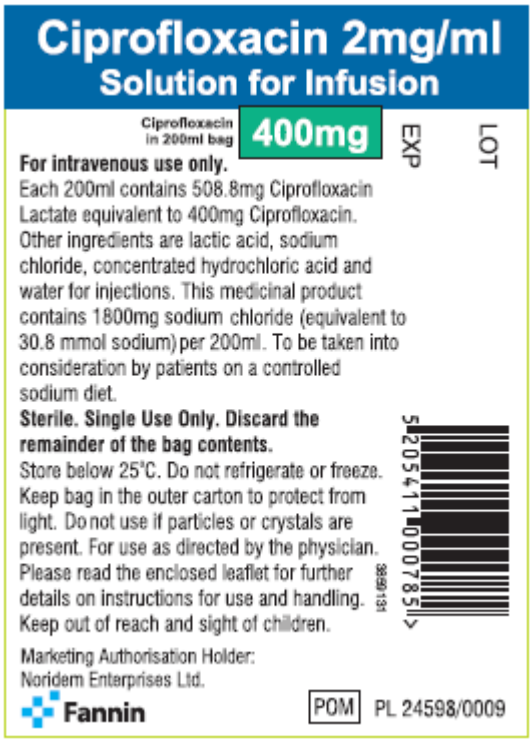
Marketing Authorisation Holder: Noridem Enterprises Ltd., Evagorou & Makariou, Mitsi Building 3, Suit.115 1065 Nicosia, Cyprus.
Manufacturer: Demo S.A., 21st km National Road Athens, Lamia, 14568 Athens, Greece.

This leaflet was prepared in July 2006

Module 4

Labelling





Module 5

Scientific discussion during initial procedure

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the application for Ciprofloxacin 2mg/mL Solution for Infusion for the treatment of infections caused by bacteria, could be approved. A national marketing authorisation was granted on 3rd October 2006.

The originator product is Ciproxin infusion 2mg/ml sterile solution for intravenous infusion (PL 00010/0150), which was licensed to Bayer plc on 16 January 1996.

With the UK as the Reference Member State in this Mutual Recognition Procedure (MRP), the Marketing Authorisation Holder, Noridem Enterprises, is applying for marketing authorisation for Ciprofloxacin 2mg/mL Solution for Infusion in Austria, Belgium, Denmark, Germany, Ireland, The Netherlands and Norway.

Ciprofloxacin is a synthetic fluorinated 4-quinolone derivative antibiotic. 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.

Ciprofloxacin is indicated for the treatment of infections when known or likely to be due to one or more susceptible micro-organisms identified in Section 5.1 of the SmPC. These include severe systemic infections, respiratory tract infections, urinary tract infections, skin, joint, bone ands soft tissue infections, eye and ear infections, intra-abdominal infections, infections of the biliary tract, gastrointestinal infections, pelvic infections and gonorrhoea.

The objective of the development programme was to develop a stable, globally acceptable solution of Ciprofloxacin comparable in performance to Ciprofloxacin Infusion 2mg/ml Sterile Solution for Intravenous Infusion (Bayer, UK), which was the reference product for this application.

No new preclinical studies were conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.

New clinical studies were not conducted, which is acceptable given that the application was based on essential similarity to a product that has been licensed for over 10 years.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

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

III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

Nomenclature

rINN: ciprofloxacin

CAS: 85721-33-1

Chemical name: 1-cyclopropyl-6-fluoro-4-oxo-7-piperazin-1-yl-quinoline-3-carboxylic acid

Structure: $C_{17}H_{18}FN_3O_3$

Molecular Mass: 331.346

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

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

Active ciprofloxacin 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
Other ingredients consist of pharmaceutical excipients, namely lactic acid, sodium chloride, concentrated hydrochloric acid and water for injections.

All excipients used comply with their respective European Pharmacopoeial monograph.
Satisfactory certificates of analysis have been provided for all excipients.

No materials of animal or human origin are contained in or used in the manufacture of these products.

Pharmaceutical Development

The aim of the pharmaceutical development was to develop a sterile solution for infusion containing the antibacterial ciprofloxacin that was essentially similar to the innovator product, Ciproxin.

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 on all batches. 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
Product is packaged in polypropylene bags with aluminium caps. Specifications and Certificates of Analysis for all packaging used have been provided. This is satisfactory. All primary product packaging comply with EU legislation regarding contact with solutions for parenteral and ophthalmic use Directive 2002/72/EC (as amended).

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions "Store below 25ºC and "Keep container in the outer carton" have been set, which are satisfactory.

Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, and pharmaceutical form. It was not necessary to demonstrate bioequivalence.

NON-CLINICAL ASSESSMENT

No new preclinical data has been supplied with this application, however a non-clinical overview summarising relevant information has been included in the MR dossier; this is satisfactory.

CLINICAL ASSESSMENT

1. INTRODUCTION

This is an application made under Article 10(1) for Ciprofloxacin 2mg/ml Solution for Infusion. The original and reference medicinal product is Ciprofloxacin Infusion 2mg/ml Sterile Solution for Intravenous Infusion (Bayer, UK).

2. BACKGROUND

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

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

3. INDICATIONS

Adults:
Treatment of infections caused by ciprofloxacin-sensitive pathogens such as:
-Infections of the respiratory tract
-Infections of the medium ear (medium otitis) and sinusitis
-Infections of the kidneys and/or the urinary tract
-Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis
-Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)
-Infections of the skin and soft tissue
-Infections of the bones and joints
-Sepsis
- Infections or risk infections (prophylaxis) in immuno-suppressed patients or with neutropenia.
-Selective intestinal decontamination in immunosuppressive patients.

Children and adolescents:
Acute pulmonary breakthrough of cystic fibrosis in children and adolescents (5 – 17 years), caused by *Pseudomonas aeruginosa*.
Ciprofloxacin is not indicated for other infections in this age group.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Inhalational Anthrax (post-exposure) in Adults and Children: To reduce the incidence or progression of disease following exposure to aerosolised *Bacillus anthracis.*

4. DOSE AND DOSE SCHEDULE

This is consistent with the originator product.

5. CLINICAL PHARMACOLOGY

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

Assessors' overall conclusions on clinical efficacy
This is acceptable for this type of application. There would be no particular concerns for a generic formulation of ciprofloxacin for intravenous use.

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

Assessor's overall conclusions on clinical safety
The safety profile of ciprofloxacin has been well established in the past. There are no particular concerns for a generic formulation provided that the safety aspects are well covered in the relevant sections of the SPC.

7. EXPERT REPORTS
A satisfactory expert report is provided by an appropriately qualified individual.

8. SUMMARY OF PRODUCT CHARACTERISTICS
The proposed SPC is satisfactory.

9. PATIENT INFORMATION LEAFLET (PIL)
The PIL is satisfactory.

10. LABEL
The label is satisfactory.

11. APPLICATION FORM
The MAA form is satisfactory.

OVERALL CONCLUSION
Grant of a marketing authorisation is recommended.

Module 5

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome
26/01/2007	Type IA	To register the trading style 'Fannin' for the marketing authorisation holder.	Granted 26/01/2007
14/02/2007	Type IA	To register the updated European Pharmacopoeia certificate of suitability	Granted 15/02/2007