Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cifox 2 mg/ml Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg Ciprofloxacin in a 50 ml solution (2mg/ml) as hydrochloride
200 mg Ciprofloxacin in a 100 ml solution (2mg/ml) as hydrochloride
400 mg Ciprofloxacin in a 200 ml solution (2mg/ml) as hydrochloride

Excipient with known effect:
Sodium 0.154 mmol (3.54mg) per 1 ml of solution.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Infusion.

A clear, sterile, aqueous solution.

pH of the solution 3.5 - 4.5

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Cifox 2 mg/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	2 to 4 weeks (acute)

		400 mg three times a day	
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice daily to 400 mg three times a day	at least 14 days
Infections of the gastro-intestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *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	6 mg/kg body weight	10 to 21 days

urinary tract infections and pyelonephritis	three times a day to 10 mg/kg body weight three times a day with a maximum of 400 mg per dose.	
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/1.73m²)	Serum Creatinine (µmol/L)	Intravenous Dose (mg)
>60	<124	See usual dose
30-60	124 to 168	200 – 400mg every 12 h
<30	>169	200 – 400mg every 24 h
Patients on haemodialysis	>169	200 – 400mg every 24h (after dialysis)
Patients on peritoneal dialysis	>169	200 -400mg every 24h

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

Children and adolescents.

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

Method of administration

Cifox should be checked visually prior to use. It must not be used if cloudy.

Ciprofloxacin should be administered by intravenous infusion.
For children, the infusion duration is 60 minutes.

In adult patients, infusion time is 60 minutes for 400 mg Ciprofloxacin and 30 minutes for 200 mg Ciprofloxacin. Slow infusion into a large vein will minimise patient discomfort and reduce the risk of venous irritation.

The infusion solution can be infused either directly or after mixing with other compatible infusion

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 Grampositive 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.
Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy.

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. Cases of status epilepticus have been reported. 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
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as for example:

- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class 1A and 111 anti-arrhytmics, tricyclic antidepressants, macrolides, antipshycotics)
- Uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia)
- Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin in these populations.

(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9)

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.

Impaired renal function:
Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

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, olanzapine, ropinirole, tizanidine, duloxetine). 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.

NaCl Load
In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account (for sodium chloride content, see section 2).

This medicinal product contains 0.154mmol or 3.54mg sodium per ml. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicines on ciprofloxacin:

Drugs known to prolong QT interval:
Ciprofloxacin like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class 1A and 111 anti-arrthymics, tricyclic antidepressants, macrolides, antipshycotics) (See section4.4).

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

Metoclopramide:
Metoclopramide accerelates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole:
Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of ciprofloxacin.

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 (Cmax 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. This may increase the risk of methotrexate associated toxic

reactions. Therefore, patients receiving methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.(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.

Ciclosporin:
A transient increase in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists:
Simultaneous administration of ciprofloxacin with warfarin may augment its anti-coagulant effects.

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 a Vit K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).

Glibenclamide:
In particular cases, concurrent administration of ciprofloxacin and glibenclamide containing medicinal products can intensify the action of glibenclamide (hypoglycaemia).

Duloxetine:
In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUG and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration (see section 4.4).

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 Cmax 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).

Lidocaine:
It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

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).

Sildenafil:
Cmax and AUC of sildenafil were increased approximately twofold in healthy Subjects after an oral dose of 50mg given concomitantly with 500mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

4.6 Fertility, 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 Bayer (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 < 1/1000	**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)	
Immune System Disorders			Allergic reaction Allergic oedema / Angio-oedema	Anaphylactic reaction Anaphylactic shock (lifethreatening) (see section 4.4) Serum sicknesslike reaction	
Metabolism and Nutrition Disorders		Anorexia	Hyperglycaemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations /thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations /thoughts or suicide attempts and completed suicide) (see section 4.4)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (incl status epilepticus 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 e.g.. diplopia	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss / Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia, torsades de pointes (reported pre-dominantly in patients with risk factors for QT pro-longation), ECG QT prolonged (see section 4.4 and 4.9)
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory,			Dyspnoea		

Thoracic and Mediastinal Disorders			(including asthmatic condition)		
Gastro-intestinal Disorders	Nausea Diarrhoea	Vomiting Gastro-intestinal 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)	Acute generalized exanthematous pustulosis (AGEP)
Musculo-skeletal, Connective Tissue and Bone Disorders		Musculo-skeletal 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 intra-venous administration)	Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalized ratio increased (in patients treated with Vitamin K antagonists)

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).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions preferably through the online reporting option accessible from the IMB homepage. A downloadable report form is also accessible from the IMB website, which may be completed manually and submitted to the IMB via ‘freepost’, in addition to the traditional post-paid ‘yellow card’ option.

FREEPOST
Pharmacovigilance Section
Irish Medicines Board
Kevin O’Malley House
Earlsfort Centre
Earlsfort Terrace
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Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.imb.ie
e-mail:imbpharmacovigilance@imb.ie

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, e.g. ventricular emptying followed by mrdical carbon,it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdose.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.
In the event of an overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolone antibacterial, ATC Code J01 MA 02

Mechanism of action

As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from both type 11 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 (Cmax) 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

Micro-organism	**Susceptible (mg/L)**	**Resistant (mg/L)**
Enterobacteria	≤0.5	>1
Pseudomonas	≤0.5	>1
Acinetobacter	≤1	>1
Staphylococcus spp[1]	≤1	>1
Haemophilus influenzae and *Moraxella catarrhalis*[3]	≤0.5	>0.5
Neisseria gonorrhoeae	≤0.03	>0.06
Neisseria meningitidis	≤0.03	>0.06
Non-species related breakpoints[4]	≤0.5	>1

1. *Staphylococcus* spp. - breakpoints for ciprofloxacin and ofloxacin relate to high dose therapy.
4. 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 (marked with -- or IE in the table).

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

Groupings of relevant species according to ciprofloxacin susceptibility

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 Cmax 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 nonionised 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.during

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	**Faeces**
Ciprofloxacin	61.5	15.2
Metabolites (M1-M4)	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 Cmax and AUC were not age-dependent (above one year of age). No notable increase in Cmax and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis Cmax 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 studies

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
Sodium Chloride
Sodium Hydroxide (pH adjuster)
Hydrochloric Acid (pH adjuster)
Water for Injections

6.2 Incompatibilities

Ciprofloxacin 2 mg/ml Solution for Infusion is not compatible with injection solutions (e.g. penicillins, heparin solutions) which are chemically or physically unstable at its pH of 3.5-4.5.
Unless compatibility is proven, the infusion should always be administered separately. For compatible co-infusion solutions see Section 6.6.

6.3 Shelf life

4 years.
Once opened use immediately.

6.4 Special precautions for storage

Keep the bottle in the outer carton in order to protect from light. 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 five days in daylight.

Do not refrigerate or freeze Ciprofloxacin 2 mg/ml Solution for Infusion. If the product is inadvertently refrigerated, crystals may form. However, these will redissolve at room temperature and do not affect the product's characteristics.

6.5 Nature and contents of container

Clear Glass Type II vials with Omniflex coated bromobutyl rubber stoppers containing 50 ml, 100 ml or 200 ml of Ciprofloxacin 2 mg/ml Solution for Infusion with aluminium crimping cap with plastic flip-off top and with a

cardboard outer.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused contents. The solution should be visually inspected prior to use and only clear solutions without particles should be used.

Ciprofloxacin 2 mg/ml Solution for Infusion should be infused directly and be administered by short-term intravenous infusion over a period of 30-60 minutes (50 ml, 100 ml) or 60 minutes (200 ml).

The product should not be mixed with other drug products which are chemically or physically unstable at its pH of 3.5-4.5 (see Section 6.2).
However, Ciprofloxacin 2 mg/ml Solution for Infusion has been shown to be compatible with 0.9% sodium chloride solution, Ringer's solution, Ringer lactate solution, 5% and 10% glucose solutions.

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

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

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Newtown
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/168/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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