Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Kuin Infusion (Ciprofloxacin 200 mg/100 ml solution)

2. Qualitative and quantitative composition

Each ml of solution for infusion contains 2 mg Ciprofloxacin as 2.544 mg Ciprofloxacin lactate

Each 100 ml vial contains 200 mg Ciprofloxacin (as Ciprofloxacin lactate).

Excipients with known effects:

Each 100ml contains 15.4 mmol (354 mg) Sodium.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion

Clear, colourless solution, free from foreign particles filled in 100 ml vial.

4. Clinical particulars

4.1 Therapeutic indications

Ciprofloxacin 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
  - in exacerbations of chronic obstructive pulmonary disease Ciprofloxacin 2mg/ml solution for infusion should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- 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
- Acute pyelonephritis

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		**Dosage**	**Total duration of treatment (including switch to oral therapy as soon as possible)**
Infections of the lower respiratory		400 mg three times a day	7 to 14 days
Infections of the upper respiratory tract	Acute exacerbation of chronic sinusitis	400 mg twice a day to 400 mg three times a day	7 to 14 days
	Chronic suppurative otitis media	400 mg twice a day 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 (see section 4.4)	Complicated and uncomplicated pyelonephritis	400 mg twice a day 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)
	Bacterial prostatitis	400 mg twice a day to 400 mg three times a day	2 to 4 weeks (acute)
Genital tract infections	Epididymo-orchitis and pelvic inflammatory diseases	400 mg twice a day to 400 mg three times a day	At least 14 days
Infections of the gastrointestinal tract and intra-abdominal infections	Diarrhoea caused by bacterial pathogens including *Shigella spp.* Other than *Shigella dysenteriae*	400 mg twice daily	1 day

	type 1 and empirical treatment of sever travellers' diarrhea		
	Diarrhea caused by *Shigella dysenteriae* type 1	400 mg twice daily	5 days
	Diarrhoea caused by *Vibrio cholera*	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 a day to 400 mg three times a day	5 to 14 days
Infections of the skin and soft tissue		400 mg twice a day to 400 mg three times a day	7 to 14 days
Bone and joint infections		400 mg twice a day to 400 mg three times a day	Max. of 3 months
Neutropenic patients with fever that is suspected to be due to a bacterial infection. Ciprofloxacin should be co-administered with appropriate antibacterial agent(s) in accordance to official guidance.		400 mg twice a day to 400 mg three times a day	Theraoy 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 oral therapy as soon as possible)**

Cystic fibrosis	10 mg/kg body weight three times aday with a maximum of 400 mg per dose.	10 to 14 days
Complicated urinary tract infections and pyelonephritis	6 mg/kg body weight three times a day to 10 mg/kg body weight three times a day with a maximum of 400mg per dose.	10 to 21 days
Inhalation anthrax post- exposure curative treatment for persons requiring parenteral treatment Drug administration should begin as soon as possible after suspected or confirmed exposure.	10 mg/kg body weight twice daily to15 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 aday with a maximum of 400 mg per dose.	According to the typeof infections

Geriatric patients

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

Renal and hepatic impairment

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

Creatinine Clearance (mL/min/1.73 m²)	**Serum Clearance (µmol/L)**	**Intravenous dose (mg)**
> 60	<124	See Usual Dosage
30-60	124 to 168	200-400 mg every 12h
< 30	>169	200-400 mg every 24h
Patients on haemodialysis	>169	200-400 mg every 24h (after dialysis)
Patients on peritoneal dialysis	>169	200-400 mg every 12h

In patients with impaired liver function no dose adjustment is required. Dosing in children with impaired renal and/or hepatic function has not been studied.

Method of administration

Ciprofloxacin 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 solutions (see section 6.2).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be coadministered 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 postsurgical 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 lifethreatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.

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

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

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

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

Gastrointestinal System

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

Renal and urinary system

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

Hepatobiliary system

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

Glucose-6-phosphate dehydrogenase deficiency

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

Resistance

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

Cytochrome P450

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, ropinirole, tizanidine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate

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

Interaction with tests

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

Injection Site Reaction
Local intravenous site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.
NaCl Load
Ciprofloxacin contains 15.1 mmol (347 mg) sodium per 100 ml solution for infusion. 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.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.
Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products 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 IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Probenecid

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

Effects of ciprofloxacin on other medicinal products:

Tizanidine
Tizanidine must not be administered together with ciprofloxacin (see section 4.3). In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (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 and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

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

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

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

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

that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with an oral anticoagulant agent.

Ropinirole
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of 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).

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 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Agomelatine
In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration ('Cytochrome P450' in section 'Special warnings and precautions for use).

Zolpidem
Co-administration ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

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 (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.

The frequencies of ADRs are defined as:
Common ≥ 1/100 to < 1/10 (≥ 1% to < 10%)
Uncommon ≥ 1/1000 to < 1/100 (≥ 0.1% to < 1%)
Rare ≥ 1/10000 to < 1/1000 (≥ 0.01% to < 0.1%)
Very rare < 1/10000 (< 0.01%)

Table 1. ADRS reported based on clinical trial data

Common **≥ 1% to < 10%**	**Uncommon** **≥ 0.1% to < 1%**	**Rare** **≥ 0.01% to < 0.1%**	**Very rare** **< 0.01%**
Infections and infestations			
	Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)	
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 /angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction
Metabolism and Nutrition Disorders			
	Decreased appetite and foodintake	Hyperglycaemia Hypoglycaemia	
Psychiatric Disorders			
	Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completedsuicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations / thoughts and attempted or completed suicide)
Nervous System Disorders			
	Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperaesthesia Intracranial hypertension (pseudotumour cerebri)
Eye Disorders			
		Visual disturbances	Visual colour distortions

Ear and Labyrinth Disorders			
		Tinnitus Hearing loss	Hearing impaired
Cardiac Disorders			
		Tachycardia	
Vascular Disorders			
		Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			
		Dyspnoea (including asthmatic condition)	
Gastrointestinal Disorders			
Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepato-biliary Disorders			
	Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to lifethreatening hepatic failure)
Skin and Subcutaneous Tissue Disorders			
	Rash Pruritis Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders			

	Arthralgia	Myalgia Arthritis Increased muscle toneand cramping	Muscular weakness Tendonitis Tendon rupture (predominantly Achillestendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders			
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitialnephritis	
General Disorders and Administration Site Conditions			
Injection and infusion site reactions (only intravenous administration) e.g phlebitis or thrombophlebitis	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations			
	Increase in blood alkaline phosphatase	Abnormal prothrombinlevel Increased amylase	

The incidence of arthropathy (arthralgia, arthritis), mentioned above, refers to data collected instudies with adults. In children, arthropathy is reported to occur commonly. ADRs derived from post marketing reports (status: 31 July 2005) and for which a frequency could not be estimated are listed in Table 2 below.

Table 2. ADR's reported based on post marketing reports

Blood and Lymphatic System Disorders	Pancytopenia (life-threatening) Bone marrow depression (life-threatening)
Immune System Disorders	Serum sickness-like reaction Anaphylactic shock (life-threatening)
Nervous System Disorders	Hyperaesthesia Intracranial hypertension Peripheral neuropathy and polyneuropathy
Cardiac Disorders**	QT prolongation Ventricular arrhythmia Torsades de pointes*
Hepato-biliary Disorders	Liver necrosis (vary rarely progressing to life-threateninghepatic failure)
Skin and Subcutaneous Tissue Disorders	Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening)Toxic epidermal necrolysis (potentially life-threatening) Acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue andBone Disorders	Exacerbation of symptoms of myasthenia gravis
General Disorders and Administration Site Conditions	Gait disturbance

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

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

Common: Vomiting, Transient increase in transaminases, Rash

Uncommon: Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Cholestatic icterus, Renal failure, Oedema

Rare: Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Olfactory nerve disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, and 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: Healthcare professionals are asked to report any suspected adverse reactions ND PQMPs to https://pv.pharmacyboardkenya.org

4.9 Overdose

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

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

In the event of 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

Mechanism of action

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

Ciprofloxacin has *in vitro* and *in vivo* activity against a wide range of gram-negative and gram-positive organisms. The bactericidal action of ciprofloxacin appears to result from interferencewith the enzyme,

DNA gyrase.

Gram-negative organisms: *Escherichia coli*; *Klebsiella* species (including *Klebsiella pneumoniae* and *Klebsiella oxytoca*); *Enterobacter* species; *Citrobacter* species; *Salmonella* species; *Shigella* species; *Proteus mirabilis*; *Proteus vulgaris*; *Providencia stuartii*; *Providencia rettgeri* (formerly *Proteus rettgeri*); *Morganella morganii* (formerly *Proteus morganii*); *Serratia* species (including *Serratia marcescens*); *Pseudomonas aeruginosa*; *Pseudomonas fluorescens*; *Haemophilus influenzae*; *Neisseria gonorrhoeae*; *Moraxella* (*Branhamella*) *catarrhalis*; *Campylobacter* species.

Gram-positive organisms*: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains); coagulase negative *Staphylococcus* species (including *Staphylococcus epidermidis*); *Streptococcus pyogenes* (group A); *Streptococcus pneumoniae*; *Enterococcus faecalis*.

*Note:

1. Gram-positive organisms and *Pseudomonas aeruginosa* are generally less sensitive to ciprofloxacin than other gram-negative organisms which results in lower drug efficacy rates.
2. Most strains of streptococci are only moderately susceptible to ciprofloxacin. Clinical studies have shown the drug to be effective for urinary tract infections caused by *Enterococcus faecalis*. Although bronchial infections caused by *Streptococcus pneumoniae* and skin infections caused by *Streptococcus pyogenes* have been shown to respond to ciprofloxacin, it is not the drug of first choice in such infections, particularly *Streptococcus pneumoniae* infection of the lower respiratory tract.
3. Most strains of *Burkholderia cepacia* and many strains of *Stenotrophomonas maltophilia* are resistant to ciprofloxacin as are most anaerobic bacteria, including *Bacteroides fragilis* and *Clostridium difficile*.
4. *Enterococcus faecium, Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant. Ciprofloxacin is ineffective against *Treponema pallidum*.
5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of ciprofloxacin.

The prevalence of resistance may vary geographically and with time for selected species andlocal information on resistance is desirable,

particularly when treating severe infections. This information gives guidance whether or not microorganisms will be susceptible to ciprofloxacin.Ciprofloxacin has been shown to be active against *Bacillus anthracis* both *in vitro* and by use of serum levels as a surrogate marker.

Ciprofloxacin is less active when tested at acidic pH and its antibacterial activity may be reduced by up to 100 fold in acidic urine. The inoculum size has little effect when tested in vitro. The minimal bactericidal concentration (MBC) is generally 2 to 8 times the minimal inhibitory concentration (MIC).

Resistance to ciprofloxacin *in vitro* develops slowly (multiple-step mutation). Rapid one-step development of resistance has not been observed. However, in practice, resistance to ciprofloxacin may develop during the course of a treatment, particularly in a significant proportion of *Pseudomonas aeruginosa* infections, especially in patients with cystic fibrosis, and in *Staphylococcus aureus* infections.

Ciprofloxacin does not exhibit cross resistance with non-quinolone antibacterial agents such as beta-lactams and aminoglycosides. However, organisms which are resistant to other quinolone agents (e.g. nalidixic acid, cinoxacin, etc) are usually less sensitive to ciprofloxacin.

In vitro studies have shown that additive activity often results when ciprofloxacin is combined with other antimicrobial agents. The combination behaves either in an indifferent or additive manner. Synergism or antagonism have been observed very rarely.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to ciprofloxacin. Therapy with ciprofloxacin may be initiated before results of these tests are known; once results become available, appropriate therapy should be continued.

Susceptibility tests

Dilution or diffusion techniques – either quantitative (Minimal Inhibitory Concentration - MIC) or breakpoint, should be used following a regularly updated, recognised and standardised method (e.g. NCCLS). Standardised susceptibility test procedures require the use of laboratory control micro-organisms to control the technical aspects of the laboratory procedures.

A report of “Susceptible” indicates that the pathogen is likely to be

inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone, which prevents small, uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Note: The prevalence of resistance may vary geographically for selected species and local information on resistance is desirable, particularly when treating severe infections.

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 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 non-ionized 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 isoenzymes.

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

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

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h. Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

<u>*Paediatric patients*</u>
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:
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

Sodium Chloride
Lactic Acid
Water for Injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Unless compatibility with other solutions/drugs has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration. Incompatibility appears with all infusion solutions/drugs that are physically or chemically unstable at the pH of the solutions (e.g. penicillins, heparin solutions), especially in combination with solutions adjusted to an alkaline pH (pH of ciprofloxacin solutions: 3.9 – 4.5).

6.3 Shelf life

For Glass vials: 2 years
After first opening: Single dose container. Use immediately after first opening.
After dilution: Use within 42 hours if diluted with the administration fluids.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage:

Store below 30℃. Do not refrigerate or freeze. Keep vial/bottle in outer carton to protect from light.

6.5 Nature and contents of container

Type II clear glass, colorless bottles with a simple thick top 32 mm rubber stopper made up of Natural Grey Rubber containing 200ml of Kuin Infusion 200mg/100ml.

Pack size: Individual vial in unit carton.

6.6 Special precautions for disposal and other handling:

Kuin infusion has been shown to be compatible with Ringer's solution, 0.9% W/V Saline NS, 5% and 10% dextrose solutions, DNS (0.9 %w/v Sodium Chloride and 5% w/v Dextrose) solution, and fructose 10% solution.

As the infusion solution is sensitive to light, only remove the bottles from the folding box for use. For single use only.

For ease of use the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Any unused solution should be disposed of.

7. Marketing authorization holder and manufacturing site addresses

Marketing authorization holder:

Pharmaken Limited,

P.O. Box 95625-80106 Mombasa,

Kenya.

Manufacturing site address:

Pharmasol Pvt. Ltd.,

Plot No. 549, Sundar Industrial Estate, Lahore,

Pakistan.

8. Marketing authorization number

CTD10825

9. Date of first registration

22/08/2023

10. Date of revision of the text:

15/09/2023

11. Dosimetry:

Not Applicable

12. Instructions for Preparation of Radiopharmaceuticals:

Not Applicable