Cifloxin™

INFUSION (2 MG/ML) SOLUTION FOR INFUSION

RODUCT NAME

CIFLOXIN INFUSION (2 MG/ML) (SOLUTION FOR INFUSION)

NAME AND STRENGTH OF ACTIVE SUBSTANCE

Each glass bottle with 100 mL infusion solution contains 200 mg of ciprofloxacin.
Each glass bottle with 200 mL infusion solution contains 400 mg of ciprofloxacin.

PRODUCT DESCRIPTION

Clear, colorless sterile solution (pH 3.5 – 4.6)

PHARMACODYNAMICS

Pharmacotherapeutic group: fluoroquinolones

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.

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.

Microbiological Susceptibility

The prevalence of acquired resistance may vary geographically and time dependent for selected species, local information on resistance is desirable, particularly when treating severe infections. Ciprofloxacin is usually active against the following microorganisms *in vitro*:-

COMMONLY SUSCEPTIBLE SPECIES		
Gram-Positive Aerobes *Bacillus anthracis*(1)		
Gram-Negative Aerobes *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*
Anaerobes *Mobiluncus*		
Others *Chlamydia trachomatis*(§) *Chlamydia pneumoniae*(§)	*Mycoplasma hominis*(§) *Mycoplasma pneumoniae*(§)	
ORGANISMS FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM		
Gram-Positive Aerobes *Enterococcus faecalis*(§)	*Staphylococcus* spp.*(2)	
Gram-Negative Aerobes *Acinetobacter baumannii* + *Burkholderia cepacia**+ *Campylobacter* spp.*+ *Citrobacter freundii** *Enterobacter aerogenes* *Enterobacter cloacae**	*Escherichia coli** *Klebsiella oxytoca* *Klebsiella pneumonia** *Morganella morganii** *Neisseria gonorrhoeae** *Proteus mirabilis**	*Proteus vulgaris** *Providencia* spp. *Pseudomonas aeruginosa** *Pseudomonas fluorescens* *Serratia marcescens**
Anaerobes *Peptostreptococcus* spp.	*Propionibacterium acnes*	
INHERENTLY RESISTANT ORGANISMS		
Gram-Positive Aerobes *Actinomyces*	*Listeria monocytogenes*	*Enteroccus faecium*
Gram-Negative Aerobes *Stenotrophomonas maltophilia*		
Anaerobes Excepted as listed above		
Others *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.

PHARMACOKINETICS

Absorption

Following an intravenous (IV) infusion of ciprofloxacin the mean maximum serum concentration (C_{max}) were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin was 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 IV dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.
A 60 minutes IV 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 minutes IV infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regards to AUC. The 400 mg IV dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.
A 60 minutes 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.

Biotransformation

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.
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 hours. 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. 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%.

INDICATION

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

Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens:

- Infections of the respiratory tract*
  Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by *Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Moraxella catarrhalis, Legionella* and *Staphylococcus*
- Infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis)* especially if these are caused by Gram-negative organisms including *Pseudomonas aeruginosa or* by staphylococci
- Infections of the eyes
- Infections of the kidneys and/or the efferent urinary tract*
- Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis*
- Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)*
- Infections of the skin and soft tissue*
- Infections of the bones and joints*
- Sepsis*
- Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)*
- Selective intestinal decontamination in immunosuppressed patients

***CIFLOXIN INFUSION (2 MG/ML) (SOLUTION FOR INFUSION)** should only be used:

- When *Pseudomonas* is considered AND the patient is allergic to antipseudomonal penicillins/cephalosporins;
- For resistant organisms with no other alternative antibiotics available

RECOMMENDED DOSAGE

General Dosage Recommendations

Adults

Indication	Recommended Dosage (IV Infusion)
Respiratory Tract Infection (according to severity and organism)	2 x 400 mg to 3 x 400 mg
Urinary Tract Infection ▪ acute, uncomplicated ▪ complicated	 2 x 200 mg to 2 x 400 mg 2 x 400 mg to 3 x 400 mg
Genital Infection ▪ adnexitis, prostatitis, epididymo-orchitis	 2 x 400 mg to 3 x 400 mg
Other Infections (See *Indication*)	2 x 400 mg
Particularly severe, life threatening infections ▪ recurrent infections in cystic fibrosis ▪ bone and joint infections ▪ septicemia ▪ peritonitis	3 x 400 mg

Special Populations

Children and Adolescents

Cystic Fibrosis

▪10 mg/kg body weight intravenous (IV) three times daily with a maximum of 400 mg per dose.

Complicated Urinary Tract Infections and Pyelonephritis

▪6 - 10 mg/kg body weight IV three times daily with a maximum of 400 mg per dose

Geriatric Patients *(> 65 years)*

- Elderly patients should receive a dose as low as possible depending on the severity of their illness and the creatinine clearance

Renal and Hepatic Impairment

Renal/Liver Function	Creatinine Clearance [mL/min/1.73m²]	Serum Creatinine [mg/100mL]	Recommended Dose (IV Infusion)
Impaired Renal Function	30 - 60	1.4 - 1.9	Maximum 800 mg daily
	< 30	≥ 2.0	Maximum 400 mg daily
Impaired Renal Function on Haemodialysis	30 - 60	1.4 - 1.9	Maximum 800 mg daily
	< 30	≥ 2.0	Maximum 400 mg daily (on dialysis days after dialysis)
Impaired renal function on continuous ambulatory peritoneal dialysis (CAPD)	-	-	Addition of ciprofloxacin infusion solution to the dialysate (intraperitoneal): 50 mg ciprofloxacin / liter dialysate given every 6 hours
Impaired liver function	-	-	No dose adjustment is required
Impaired renal and liver function	30 - 60	1.4 - 1.9	Maximum 800 mg daily
	< 30	≥ 2.0	Maximum 400 mg daily

[Note: Dosing in children with impaired renal and or hepatic function has not been studied]

ROUTE OF ADMINISTRATION

Intravenous infusion

Method of administration

If the patient is unable to take ciprofloxacin film-coated tablets because of the severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration, the treatment can be continued orally.

Intravenous infusion

Ciprofloxacin should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with other compatible infusion solutions (See *Incompatibilities*).

Duration of treatment

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms.

Mean duration of treatment

- 1 day for acute uncomplicated gonorrhea and cystitis
- Up to 7 days for infections of the kidneys, urinary tract and abdominal cavity
- Over the entire period of the neutropenic phase in patients with weakened body defenses
- A maximum of 2 months in osteomyelitis
- 7-14 days in all other infections
- At least 10 days for streptococcal infections due to the risk of late complications
- A minimum of 10 days for infections caused by *Chlamydia* spp.

Children and adolescents

- Cystic fibrosis, for broncho-pulmonary infections associated with *Pseudomonas aeruginosa* in pediatric patients (aged 5-17 years), the duration of treatment is 10-14 days
- Complicated urinary tract infections and pyelonephritis due to *Escherichia coli*, the duration of treatment is 10–21 days

CONTRAINDICATIONS

Hypersensitivity to the active substance, to other quinolones or to any of the excipients.
Concomitant administration of ciprofloxacin and tizanidine (see I*nteraction with Other Medicinal Products / Other Forms of Interaction*).

WARNINGS AND PRECAUTIONS

The use of ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see Undesirable Effects). Treatment of these patients with ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit / risk assessment.

Aortic aneurysm and dissection

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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin should be advised to inform their doctor and pharmacist prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition (see Undesirable Effects).

Exacerbation of myasthenia gravis

Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Severe infections and mixed infections with gram-positive and anaerobic pathogens

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

Drawing No. CIF-INF-50-100-200-03-L-ENG-MY-A0001 Sent date 20/05/2020

back

29.7 cm

21 cm

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* isolates.
For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.
NaCl load
In patients for whom sodium intake is of medical concern (e.g. patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account.
Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
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.
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. In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.
Injection site reaction
Local intravenous (IV) site reactions have been reported following IV 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 IV administration is not contraindicated unless the reactions recur or worsen.
Paediatric population
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. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.
Interaction with tests
Ciprofloxacin *in vitro* potency may interfere with the *Mycobacterium* spp. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking ciprofloxacin.

INTERACTION WITH OTHER MEDICINAL PRODUCTS / OTHER FORMS OF INTERACTION
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.
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.
Cyclosporin
A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin were administered simultaneously. Therefore, it is necessary to control the patient serum creatinine concentrations frequently (twice a week).
Probenecid
Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases the ciprofloxacin serum concentrations.
Tizanidine
Serum tizanidine concentration increased when given concomitantly with ciprofloxacin. The increased of tizanidine plasma concentration is associated with a potentiated hypotensive and sedative effect. Therefore, tizanidine must not be administered together with ciprofloxacin.
Duloxetine
Concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase serum concentration of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.
Clozapine
Serum concentrations of clozapine and *N*-desmethylclozapine were increased, following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised.
Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products, raised serum concentrations of these xanthine derivatives were reported.
Vitamin K antagonists
Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalized ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon, or fluindione).
Sildenafil
Serum concentration of sildenafil was increased approximately 2-fold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used when prescribing ciprofloxacin concomitantly with sildenafil, taking into consideration the risks and the benefits.

PREGNANCY AND LACTATION
Pregnancy
It cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus. As a precautionary measure, ciprofloxacin should not be used 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.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINE
Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

UNDESIRABLE EFFECTS
Summary of Safety Profile
The most common reported adverse reactions are nausea, diarrhoea, vomiting, transient increase in transaminases, rash, injection and infusion site reactions. The adverse reactions presented below are classified by system organ from both oral and intravenous administration of ciprofloxacin.

System Organ	Frequency	Adverse Reactions
Infections and infestations	Uncommon	: Mycotic superinfections
Blood and lymphatic system disorders	Uncommon Rare Very rare	: Eosinophilia : Leukopenia, neutropenia, thrombocytopenia, thrombocytaemia, leukocytosis, anaemia : Haemolytic, anaemia, agranulocytosis, bone marrow depression and pancytopenia *(life-threatening)*
Immune system disorders	Rare Very rare	: Allergic reaction, allergic oedema/angioedema : Anaphylactic reaction, serum sickness-like reaction, anaphylactic shock *(life-threatening)*
Metabolism and nutrition disorders	Uncommon Rare	: Decreased appetite : Hyperglycaemia, hypoglycemia
Psychiatric disorders*	Uncommon Rare Very rare Not known	: Psychomotor hyperactivity/agitation : Confusion and disorientation, anxiety reaction, abnormal dreams, depression, hallucination : Psychotic reactions (i.e. suicidal ideations/thoughts or suicide attempts and completed suicide) : Mania, including hypomania
Nervous system disorders*	Uncommon Rare Very rare Not known	: Headache, taste disorders, sleep disorders, dizziness : Par- and Dysaesthesia, hypoaesthesia, tremor, vertigo, seizures (including status epilepticus) : Migraine, disturbed coordination, smell disorders, intracranial hypertension and pseudotumor cerebri : Peripheral neuropathy and polyneuropathy
Eye disorders*	Rare Very rare	: Visual disturbances (e.g. diplopia) : Visual colour distortions
Ear and labyrinth disorders*	Rare	: Tinnitus, hearing loss/impaired
Cardiac disorders	Rare Not known	: Tachycardia : Ventricular arrhythmia, ECG QT prolonged, torsades de pointes *(predominant in patient with risk for QT prolongation)*
Vascular disorders	Rare Very rare	: Vasodilatation, hypotension, syncope : Vasculitis
Respiratory, thoracic and mediastinal disorders	Rare	: Dyspnoea (including asthmatic condition)
Gastrointestinal disorders	Common Uncommon Rare Very rare	: Nausea, diarrhoea : Vomiting, gastrointestinal and abdominal pains, dyspepsia, flatulence : Antibiotic associated colitis : Pancreatitis
Hepatobiliary disorders	Uncommon Rare Very rare	: Increase in transaminases, increased bilirubin : Hepatic impairment, jaundice, hepatitis (non-infective) : Liver necrosis (very rarely progressing to life threatening hepatic failure)
Skin and subcutaneous tissue disorders	Uncommon Rare Very rare Not known	: Rash, pruritus, urticarial : Photosensitivity reactions : Petechiae, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis : Acute Generalized Exanthematous Pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and connective tissue disorders*	Uncommon Rare Very rare	: Arthralgia, musculoskeletal pain : Myalgia, arthritis, increased muscle tone and cramp : Muscular weakness, tendinitis, tendon rupture, exacerbation of myasthenia gravis *(post marketing experience)*
Renal and urinary disorders	Uncommon Rare	: Renal Impairment : Renal failure, tubulointerstitial nephritis, haematuria, crystalluria
General disorders and administration site conditions*	Common Uncommon Rare	: Injection and infusion site reactions (only IV route) : Asthenia, fever : Oedema, sweating (hyperhidrosis)
Investigations	Uncommon Rare Not known	: Increase in blood alkaline phosphatase : Increased amylase : International normalized ratio increased (in patients treated with Vitamin K antagonists)

Remark
*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors (see *Warnings and Precautions*).

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, jaundice, renal failure, oedema
Rare	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impaired, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

Paediatric Population
The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

OVERDOSE AND TREATMENT
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 medical carbon), it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.
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.

COMPATIBILITIES
The ciprofloxacin infusion solution is compatible with Ringer solution, Ringer lactate solution, 5% and 10% glucose solutions, 5% and 10% fructose solutions. When ciprofloxacin infusion solutions are mixed with compatible infusion solutions, for microbial reasons and light sensitivity these solutions must be administered shortly after admixture.

INCOMPATIBILITIES
This medicinal product must not be mixed with other medicinal products, unless compatibility with other infusion solutions/drugs has been confirmed, the infusion solution must always be administered separately. Examples of the visual signs of incompatibility are 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-value of Cifloxin Infusion ranges from 3.5 to 4.6).

STORAGE CONDITIONS
Do not store above 30°C.
Protect from light and avoid freezing.
Keep the vial in the packaging box until time of use in order to protect from light.

SHELF LIFE
2 years

DOSAGE FORMS AND PACKAGING AVAILABLE
Cifloxin Infusion (200 mg per 100 mL) : 1 glass bottle of 100 mL sterile solution per unit box
Cifloxin Infusion (400 mg per 200 mL) : 1 glass bottle of 200 mL sterile solution per unit box

DATE OF REVISION OF PI
Date of revision: 11/05/2020

Manufacturer:- SIAM BHEASACH CO., LTD.
123 Soi Chokechairuammitr, Vibhavadi-Rangsit Road, Chomphon, Chatuchak, Bangkok 10900
and 9 Soi Chokechairuammitr 3, Vibhavadi-Rangsit Road, Dindang, Dindang, Bangkok 10400, Thailand.

Product Registration Holder, Importer:- SPG PHARMA (MALAYSIA) SDN. BHD.
Suite 1701, Block A, Damansara Intan e-Business Park,
No. 1, Jalan SS20/27, 47400 Petaling Jaya, Selangor Darul Ehsan, Malaysia.

CIF-INF-50-100-200-03-L-ENG-MY-A0001

Drawing No. CIF-INF-50-100-200-03-L-ENG-MY-A0001 Sent date 20/05/2020