Injection U.S.P.(Ciprofloxacin)

CIFIN I.V

(Ciprofloxacin)
For intravenous infusion
Rx only

apdl

WARNING:

Fluoroquinolones, including CIFIN IV, are associated with an increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants (see WARNINGS).

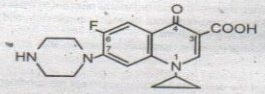
Fluoroquinolones, including CIFIN IV, may exacerbate muscle weakness in persons with myasthenia gravis. Avoid CIFIN IV in patients with known history of myasthenia gravis (see WARNINGS).

COMPOSITION

Each 100ml contains:
Ciprofloxacin USP 200mg
Sodium Chloride USP ..... 0.9 % w/v
Water for injection USP ..... q.s

DESCRIPTION

Ciprofloxacin Injection, USP is a synthetic broad-spectrum antimicrobial agent for intravenous (I.V.) administration. Ciprofloxacin, a fluoroquinolone, is 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, its empirical formula is $C_{17}H_{18}FN_3O_3$ and its chemical structure is:



Ciprofloxacin is a faint to light yellow crystalline-powder with a molecular weight of 331.4. It is soluble in dilute (0.1N) hydrochloric acid and is practically insoluble in water and ethanol.

CLINICAL PHARMACOLOGY

Absorption

Following 60-minute intravenous infusions of 200 mg and 400 mg ciprofloxacin to normal volunteers, the mean maximum serum concentrations achieved were 2.1 and 4.6 mcg/mL, respectively; the concentrations at 12 hours were 0.1 and 0.2 mcg/mL, respectively.

Steady-state Ciprofloxacin Serum Concentrations (mcg/mL) After 60-minute I.V. Infusions q 12 h.

	Time after starting the infusion					
Dose	30 min.	1 hr	3 hr	6 hr	8 hr	12 hr
200 mg	1.7	2.1	0.6	0.3	0.2	0.1
400 mg	3.7	4.6	1.3	0.7	0.5	0.2

The pharmacokinetics of ciprofloxacin are linear over the dose range of 200 to 400 mg administered intravenously. Comparison of the pharmacokinetic parameters following the 1st and 5th I.V. dose on a q 12 h regimen indicates no evidence of drug accumulation.
An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours has been shown to produce an area under the serum concentration time curve (AUC) equivalent to that produced by a 500 mg oral dose given every 12 hours. An intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 8 hours has been shown to produce an AUC at steady-state equivalent to that produced by a 750 mg oral dose given every 12 hours. A 400 mg I.V. dose results in a Cmax similar to that observed with a 750 mg oral dose. An infusion of 200 mg ciprofloxacin given every 12 hours produces an AUC equivalent to that produced by a 250 mg oral dose given every 12 hours.

Distribution

After intravenous administration, ciprofloxacin is present in saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile, and prostatic secretions. It has also been detected in the lung, skin, fat, muscle, cartilage, and bone. Although the drug diffuses into cerebrospinal fluid (CSF), CSF concentrations are generally less than 10% of peak serum concentrations. Levels of the drug in the aqueous and vitreous chambers of the eye are lower than in serum.

Metabolism

After I.V. administration, three metabolites of ciprofloxacin have been identified in human urine which together account for approximately 10% of the intravenous dose. The binding of ciprofloxacin to serum proteins is 20 to 40%.
Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism. Co-administration of ciprofloxacin with other drugs primarily metabolized by CYP1A2 results in increased plasma concentrations of these drugs and could lead to clinically significant adverse events of the co-administered drug (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS: Drug Interactions.)

Excretion

The serum elimination half-life is approximately 5 to 6 hours and the total clearance is around 35 L/hr. After intravenous administration, approximately 50% to 70% of the dose is excreted in the urine as unchanged drug. Following a 200 mg I.V. dose, concentrations in the urine usually exceed 200 mcg/mL 0 to 2 hours after dosing and are generally greater than 15 mcg/mL 8 to 12 hours after dosing. Following a 400 mg I.V. dose, urine concentrations generally exceed 400 mcg/mL 0 to 2 hours after dosing and are usually greater than 30 mcg/mL 8 to 12 hours after dosing. The renal clearance is approximately 22 L/hr. The urinary excretion of ciprofloxacin is virtually complete by 24 hours after dosing.

- to treat non-bacterial infections, e.g. non-bacterial (chronic) prostatitis;
- for preventing traveller's diarrhoea or recurring lower urinary tract infections (urine infections that do not extend beyond the bladder);
- to treat mild or moderate bacterial infections unless other antibacterial medicines commonly recommended for these infections cannot be used.

DRUG INTERACTIONS

As with some other quinolones, ciprofloxacin interacts with theophylline, caffeine, cyclosporine, phenytoin, glyburide, oral anticoagulant warfarin or its derivatives, probenecid and methotrexate. Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

DOSAGE AND ADMINISTRATION - ADULTS

CIFIN I.V should be administered to adults by intravenous infusion over a period of 60 minutes at dosages described in the Dosage Guidelines table.

ADULTS - DOSAGE GUIDELINES

Infection	Severity	Dose	Frequency	Usual Duration
Urinary Tract	Mild/Moderate	200 mg	q12h	7 to 14 Days
	Severe/Complicated	400 mg	q12h	7 to 14 Days
Lower Respiratory Tract	Mild/Moderate	400 mg	q12h	7 to 14 Days
	Severe/Complicated	400 mg	q8h	7 to 14 Days
Nosocomial Pneumonia	Mild/Moderate/Severe	400 mg	q8h	10 to 14 Days
Skin and Skin Structure	Mild/Moderate	400 mg	q12h	7 to 14 Days
	Severe/Complicated	400 mg	q8h	7 to 14 Days
Bone and Joint	Mild/Moderate	400 mg	q12h	≥ 4 to 6 Weeks
	Severe/Complicated	400 mg	q8h	≥ 4 to 6 Weeks
Intra-Abdominal*	Complicated	400 mg	q12h	7 to 14 Days
Acute Sinusitis	Mild/Moderate	400 mg	q12h	10 Days
Chronic Bacterial Prostatitis	Mild/Moderate	400 mg	q12h	28 Days
Empirical Therapy in Febrile Neutropenic Patients	Severe Ciprofloxacin + Piperacillin	400 mg 50 mg/kg Not to exceed 24 g/day	q8h q4h	7 to 14 Days

Microbiology

Ciprofloxacin has in vitro activity against a wide range of gram-negative and gram-positive microorganisms. The bactericidal action of ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase I.V., which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, micro-organisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. There is no known cross-resistance between ciprofloxacin and other classes of antimicrobials. In vitro resistance to ciprofloxacin develops slowly by multiple step mutations.
For susceptible microorganisms see the INDICATIONS AND USAGE section of the package insert for ciprofloxacin Injection, USP.

INDICATIONS AND USAGE

CIFIN I.V is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions and patient populations listed below when the intravenous administration offers a route of administration advantageous to the patient. Please see DOSAGE AND ADMINISTRATION for specific recommendations.

Adult Patients:

Urinary Tract Infections caused by *Escherichia coli* (including cases with secondary bacteremia), *Klebsiella pneumoniae* subspecies *pneumoniae, Enterobacter cloacae, Serratiamarcescens, Proteus mirabilis, Providenciarettgeri, Morganellamorganii, Citrobacterdiversus, Citrobacterfreundii, Pseudomonas aeruginosa, methicillin-susceptible Staphylococcus epidermidis, Staphylococcus saprophyticus, or Enterococcus faecalis.*

Lower Respiratory Infections caused by *Escherichia coli,Klebsiellapneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas* aeruginosa, Haemophilusinfluenzae,Haemophilus(give space)parainfluenzae, or penicillin-susceptible Streptococcus pneumoniae. Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*
Nosocomial Pneumonia caused by Haemophilusinfluenzae or Klebsiellapneumoniae.
Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiellapneumoniae , Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providenciastuartii, Morganellamorganii, Citrobacterfreundii, Pseudomonas aeruginosa, methicillin-susceptible Staphylococcus aureus,* methicillin-susceptible *Staphylococcus epidermidis, or Streptococcus pyogenes.*
Bone and Joint Infections caused by Enterobacter cloacae, Serratiamarcescens, or Pseudomonas aeruginosa.
Complicated Intra-Abdominal Infections (used in conjunction with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiellapneumoniae, or Bacteroidesfragilis.*
Acute Sinusitis caused by Haemophilusinfluenzae, penicillin-susceptible Streptococcus pneumoniae, or Moraxella catarrhalis.
Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*
Empirical Therapy for Febrile Neutropenic Patients in combination with piperacillin sodium.

Pediatric Patients (1 to 12 years of age)
Complicated Urinary Tract Infections and Pyelonephritis due to Escherichia coli:
NOTE: Although effective in clinical trials, ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse events compared to controls, including events related to joints and/or surrounding tissues. Ciprofloxacin, like other fluoroquinolones, is associated with arthropathy and histopathological changes in weight-bearing joints of juvenile animals.

CONTRAINDICATIONS

CIFIN I.V is contraindicated in persons with history of hypersensitivity to ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.
Pregnant Women: THE SAFETY AND EFFECTIVENESS OF CIPROFLOXACIN IN PREGNANT WOMEN, AND LACTATING WOMEN HAVE NOT BEEN ESTABLISHED.
Pediatrics: Ciprofloxacin should be used in pediatric patients (less than 12 years of age) only for the infections listed in the INDICATIONS AND USAGE section.
Co-administration of ciprofloxacin and other drugs primarily metabolized by the CYP1A2 (e.g., theophylline, methylxanthines, tizanidine) results in increased plasma concentrations of the co-administered drug and could lead to clinically significant pharmacodynamic side effects of the co-administered drug.
Central Nervous System Disorders: Convulsions, increased intracranial pressure and toxic psychosis have been reported in patients receiving quinolones, including ciprofloxacin. Ciprofloxacin may also cause central nervous system (CNS) events including: dizziness, confusion, tremors, hallucinations, depression, and, rarely, suicidal thoughts or acts. These reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. As with all quinolones, ciprofloxacin should be used with caution in patients with known or suspected CNS disorders that may predispose to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy), or in the presence of other risk factors that may predispose to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction).

WARNINGS

Tendinopathy and Tendon Rupture

Fluoroquinolones, including CIFIN IV, are associated with increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney,heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independentlyincrease the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Inflammation and tendon rupture can occur, sometimes bilaterally, even within the first 48 hours, during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. CIFIN IV should be used with caution in patients with a history of tendon disorders. CIFIN IV should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

Exacerbation of Myasthenia Gravis

Fluoroquinolones, including CIFIN IV, have neuromuscular blocking activity and may exacerbate muscle weakness in persons with myasthenia gravis. Postmarketing serious adverse events, including deaths and requirement for ventilatory support, have been associated with fluoroquinolone use in persons with myasthenia gravis. Avoid CIFIN in patients with known history of myasthenia gravis **(See PRECAUTIONS: Information for Patients and ADVERSE REACTIONS: Postmarketing Adverse Event Reports.)**

ADVERSE REACTIONS

The most frequently reported drug related events, from clinical trials of all formulations, all dosages, all drug-therapy durations, and for all indications of ciprofloxacin therapy are nausea, diarrhea, liver function tests abnormal, vomiting, and rash, central nervous system disturbance, local I.V. site reactions, eosinophilia, headache, restlessness, and rash. Many of these events are described as only mild or moderate in severity, Additional medically important events, without regard to drug relationship or route of administration are listed below:

BODY AS A WHOLE: abdominal pain/discomfort, foot pain, pain, pain in extremities

CARDIOVASCULAR: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, palpitation, cerebral thrombosis, syncope, cardiac murmur, hypertension, hypotension, angina pectoris, atrial flutter, ventricular ectopy, (thrombo)-phlebitis, vasodilation, migraine

CENTRAL NERVOUS SYSTEM: convulsive seizures, paranoia, toxic psychosis, depression, dysphasia, phobia, depersonalization, manic reaction, unresponsiveness, ataxia, confusion, hallucinations, dizziness, lightheadedness, paresthesia, anxiety, tremor, insomnia, nightmares, weakness, drowsiness, irritability, malaise, lethargy, abnormal gait, grand mal convulsion, anorexia

GASTROINTESTINAL: ileus, jaundice, gastrointestinal bleeding, C. difficile associated diarrhea, pseudomembranous colitis, pancreatitis, hepatic necrosis, intestinal perforation, dyspepsia, epigastric pain, constipation, oral ulceration, oral candidiasis, mouth dryness, anorexia, dysphagia, flatulence, hepatitis, painful oral mucosa

HEMIC/LYMPHATIC: agranulocytosis, prolongation of prothrombin time, lymphadenopathy, petechia

METABOLIC/NUTRITIONAL: amylase increase, lipase increase

MUSCULOSKELETAL: arthralgia, jaw, arm or back pain, joint stiffness, neck and chest pain, achiness, flare up of gout, myasthenia gravis

RENAL/UROGENITAL: renal failure, interstitial nephritis, nephritis, hemorrhagic cystitis, renal calculi, frequent urination, acidosis, urethral bleeding, polyuria, urinary retention, gynecomastia, candiduria, vaginitis, breast pain. Crystalluria, cylindruria, hematuria and albuminuria have also been reported

RESPIRATORY: respiratory arrest, pulmonary embolism, dyspnea, laryngeal or pulmonary edema, respiratory distress, pleural effusion, hemoptysis, epistaxis, hiccough, broncospasm

SKIN/HYPERSENSITIVITY: allergic reactions, anaphylactic reactions including life-threatening anaphylactic shock, erythema multiforme/Stevens-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, angioedema, edema of the lips, face, neck, conjunctivae, hands or lower extremities, purpura, fever, chills, flushing, pruritus, urticaria, cutaneous candidiasis, vesicles, increased perspiration, hyperpigmentation, erythema nodosum, thrombophlebitis, burning, paresthesia, erythema, swelling, photosensitivity/phototoxicity reaction. (See WARNINGS.

SPECIAL SENSES: decreased visual acuity, blurred vision, disturbed vision (flashing lights, change in color perception, overbrightness of lights, diplopia), eye pain, anosmia, hearing loss, tinnitus, nystagmuschromatopsia, a bad taste

OVERDOSAGE

In the event of acute overdosage, the patient should be carefully observed and given supportive treatment, including monitoring of renal function. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (<10%) is removed from the body after hemodialysis or peritoneal dialysis.

PRECAUTIONS

Intravenous ciprofloxacin should be administered by slow infusion over a period of 60 minutes. Local I.V. site reactions have been reported with the intravenous administration of ciprofloxacin. These reactions are more frequent if infusion time is 30 minutes or less or if small veins of the hand are used.

Alkalinity of the urine should be avoided in patients receiving ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Renal Impairment: Alteration of the dosage regimen is necessary for patients with impairment of renal function. (See DOSAGE AND ADMINISTRATION.)

Photo-toxicity: Excessive exposure to light should be avoided and therapy should be discontinued if photo-toxicity occurs

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic, is advisable during prolonged therapy.

Restrictions on the use of fluoroquinolone antibiotics will mean that they should not be used:

- to treat infections that might get better without treatment or are not severe (such as throat infections);

Conversion of I.V. to Oral Dosing in Adults: Parenteral therapy may be switched to oral ciprofloxacin when the condition warrants, at the discretion of the physician. (See table below for the equivalent dosing regimens.)

Equivalent AUC Dosing Regimens	Equivalent
Ciprofloxacin Oral Dosage	CIFIN I.V Dosage
250 mg Tablet q 12 h	200 mg I.V. q 12 h
500 mg Tablet q 12 h	400 mg I.V. q 12 h
750 mg Tablet q 12 h	400 mg I.V. q 8 h

parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Presentation

Clear, colourless solution in sterile plastic bottle of 100ml

Shelf life

The manufacturing and expiry dates are indicated on the packaging.

Storage

Store below 30° C but do not freeze, protect from light.

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