

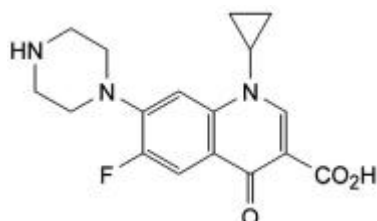
PRODUCT INFORMATION

ASPEN CIPROFLOXACIN Injection for Intravenous Infusion

NAME OF THE DRUG

Ciprofloxacin

The chemical structure is shown below:



DESCRIPTION

Aspen Ciprofloxacin Injection for Intravenous Infusion is a synthetic carboxyquinolone derivative with broad spectrum antimicrobial activity for intravenous (IV) administration.

Ciprofloxacin, a fluoroquinolone, is a 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is C₁₇H₁₈FN₃O₃ and it has a molecular weight of 331.4 (CAS registry number 85721-33-1). Ciprofloxacin is a faint to light yellow crystalline powder.

Aspen Ciprofloxacin Injection for Intravenous Infusion is available as a ciprofloxacin (as lactate) 100 mg/50 mL and a 200 mg/100 mL infusion solution. It also contains the excipients lactic acid (as a solubilising agent), glucose (55 mg/mL) and water for injections. Aspen Ciprofloxacin Injection for Intravenous Infusion is a clear, colourless to a slightly yellowish solution.

PHARMACOLOGY

Pharmacokinetics

Distribution

Immediately following a 30 minute intravenous infusion of 200 mg ciprofloxacin, serum concentrations average 3 microgram/mL. During the first hour after completion of infusion, serum concentration decreases to approximately 30% of the peak value, but thereafter serum concentrations decline with a half life of approximately four hours. Mean concentrations observed after a 200 mg dose are given below:

Ciprofloxacin serum concentrations (microgram/mL) after a 30 minute infusion							
Dose	End of Infusion	0.5 hr	1 hr	3 hr	6 hr	8 hr	12 hr
200 mg	3.18	1.4	1.0	0.5	0.3	0.2	0.1

The pharmacokinetics of intravenously administered ciprofloxacin are near linear over the dosage range of 100 mg to 300 mg, as no substantial dose dependent changes in clearance or serum half life are observed.

Approximately 50 to 70% of the intravenous dose is excreted in the urine as unchanged drug. During the first two hours of a 200 mg intravenous dose, the urine concentration of ciprofloxacin usually exceeds 200 microgram/mL.

Metabolism

Four metabolites, desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4), have been identified in human urine which, together, account for approximately 12% of an intravenous dose. The metabolites have less antimicrobial activity than unchanged ciprofloxacin.

Excretion

Urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin is approximately 18 L/hr which exceeds the normal glomerular filtration rate of 7.2 L/hr. Thus, active tubular secretion would seem to play a significant role in its elimination.

Although bile concentrations of ciprofloxacin are 3 to 4 times higher than serum concentrations after intravenous dosing, only a small amount of the dose administered (< 1%) is recovered from bile as unchanged drug.

An additional 1 to 2% of the dose is recovered from bile in the form of metabolites.

Approximately 15% of an intravenous dose is recovered from the faeces within five days after dosing.

Protein binding

Binding of ciprofloxacin to serum protein is 20 to 40%.

Factors influencing pharmacokinetics

Impaired renal/hepatic function

In patients with creatinine clearance between 21 to 40 mL/min, the half life of ciprofloxacin is slightly prolonged, but dosage adjustments are usually not required in such cases. However, in patients with severe renal impairment, with creatinine clearance less than 20 mL/min, the half life of ciprofloxacin is nearly doubled and dosage adjustment is necessary (see **DOSAGE AND ADMINISTRATION**). Serum metabolite concentrations, particularly sulfociprofloxacin (M2) and oxociprofloxacin (M3), are higher in renally impaired patients than in patients with normal renal function.

In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics were observed. The kinetics of ciprofloxacin in patients with acute hepatic insufficiency, however, have not been fully elucidated.

Age (elderly)

The higher levels of ciprofloxacin and its metabolites seen in elderly patients are possibly due to reduced renal function and volume of distribution.

Inhalational anthrax

The mean serum concentrations of ciprofloxacin associated with a statistically significant improvement in survival in the rhesus monkey model of inhalational anthrax are reached or exceeded in adult and paediatric patients receiving oral and intravenous regimens (see **DOSAGE AND ADMINISTRATION**). Ciprofloxacin pharmacokinetics have been evaluated in various human populations. The mean peak serum concentration achieved at steady state in human adults receiving 500 mg orally every 12 hours is 2.97 microgram/mL, and 4.56 microgram/mL following 400 mg intravenously every 12 hours. The mean trough serum concentration at steady state for both of these regimens is 0.2 microgram/mL. In a study of 10 paediatric patients between 6 and 16 years of age, the mean peak plasma concentration achieved is 8.3 microgram/mL and trough concentrations range from 0.09 to 0.26 microgram/mL, following two 30 minute intravenous infusions of 10 mg/kg administered 12 hours apart. After the second intravenous infusion, patients switched to 15 mg/kg orally every 12 hours achieve a mean peak concentration of 3.6 microgram/mL after the initial oral dose. Long term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited. (For additional information, see **PRECAUTIONS – Use in paediatrics**.) Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

A placebo controlled animal study in rhesus monkeys exposed to an inhaled mean dose of 11 LD₅₀ (~5.5 x 10⁵) spores (range 5 to 30 LD₅₀) of *B. anthracis* was conducted. The minimal inhibitory concentration (MIC) of ciprofloxacin for the anthrax strain used in this study was 0.08 microgram/mL. In the animals studied, mean serum concentrations of ciprofloxacin achieved at expected T_{max} (one hour post-dose) following oral dosing to steady state ranged from 0.98 to 1.69 microgram/mL. Mean steady state trough concentrations at 12 hours post-dose ranged from 0.12 to 0.19 microgram/mL. Mortality due to anthrax for animals that received a 30 day regimen of oral ciprofloxacin beginning 24 hours post-exposure was significantly lower (1/9), compared to the placebo group (9/10) [p= 0.001]. The one ciprofloxacin treated animal that died of anthrax did so following the 30 day drug administration period.

Pharmacokinetic drug interactions

The potential for pharmacokinetic drug interactions between ciprofloxacin and theophylline, caffeine, cyclosporin, sulfonyleurea, warfarin, probenecid, and methotrexate has been evaluated (See **PRECAUTIONS: Interactions with other drugs**).

Microbiology

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 interference with 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. *Ureaplasma urealyticum* and *Nocardia asteroides* are generally resistant.
5. The *in vitro* MIC of several strains of *Serratia* approaches or exceeds the peak plasma concentrations with the recommended doses of 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.

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 (eg. 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.

INDICATIONS

Aspen Ciprofloxacin Injection for Intravenous Infusion is indicated for use in the following:

1. Hospitalised adult patients in whom oral ciprofloxacin is indicated but cannot be administered or where the oral form is inappropriate.
2. For the treatment of serious or life threatening infections due to sensitive organisms involving the following organ systems:
 - Lower respiratory tract infections (gram-negative organisms)
 - Skin and skin structure
 - Septicaemia
 - Bone and joint
 - Urinary tract
3. Inhalational anthrax (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*. Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication.

Note: Because gram-positive organisms are generally less sensitive to ciprofloxacin, it may not be the drug of choice in cases with gram-positive infections due to *Streptococcus pneumoniae*.

If anaerobic organisms are suspected of contributing to the infection, use of other suitable drugs should be considered.

Strains of *Neisseria gonorrhoea* resistant to ciprofloxacin have been reported in Australia.

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.

Ciprofloxacin is suitable to treat mixed infections caused by susceptible strains of both gram-negative and gram-positive aerobic bacteria. If anaerobic organisms are suspected as accompanying aetiologic agents, additional therapy should be considered.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or other quinolones (including nalidixic acid) is a contraindication to its use.

PRECAUTIONS

The use of ciprofloxacin in pre-pubertal children [except for use in inhalational anthrax (post-exposure)] and during pregnancy is not recommended.

Increased toxicity of intravenous ciprofloxacin has been associated with increased duration of use, hence oral ciprofloxacin should be substituted as soon as practicable.

Although clinical improvement has been observed in patients with respiratory exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa*, bacterial eradication is usually not achieved. Resistance to ciprofloxacin has been shown to develop in a significant proportion of *Pseudomonas aeruginosa* infections in cystic fibrosis patients following a single course of the drug.

As with other broad spectrum antimicrobial agents, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Colitis: Antibiotic associated pseudomembranous colitis has been reported with many antibiotics including ciprofloxacin. A toxin produced by *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However in moderate to severe cases, appropriate therapy such as oral antibacterial agents effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g. opiates and diphenoxylate with atropine (Lomotil), may prolong and/or worsen the condition and should not be used.

Hypersensitivity Reactions: Serious, and occasionally fatal hypersensitivity (anaphylactoid) reactions, some following the first dose, have been reported in patients receiving quinolones (including ciprofloxacin). Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnea, urticaria and itching. Appropriate emergency measures for the management of such reactions should be readily available.

Severe hypersensitivity reactions characterized by rash, fever, eosinophilia, jaundice, and hepatic necrosis with fatal outcome have also been reported extremely rarely in patients receiving ciprofloxacin along with other drugs. The possibility that these reactions were related to ciprofloxacin cannot be excluded. Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity.

Phototoxicity: Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic and other quinolone antibiotics, produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Crystalluria: The solubility of ciprofloxacin is pH dependent and is greatly reduced between pH 5 and 9. Crystals of ciprofloxacin have been observed in the urine of laboratory animals given high doses of the drug, but also in some patients receiving standard therapeutic doses. Crystalluria seems to occur under alkaline conditions of the urine and is less likely in non-vegetarians who usually have an acidic urine. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. It should, however, be noted that the activity of ciprofloxacin is significantly reduced in acid media.

Central Nervous System (CNS) Disorders: As with other quinolones, ciprofloxacin may cause central nervous system (CNS) stimulation which may lead to transient tremor, restlessness, dizziness, light headedness, confusion, and very rarely to hallucinations or convulsive seizures. These reactions may occur following the first dose. If these reactions do occur in patients receiving ciprofloxacin, the drug should be discontinued and appropriate measures instituted. Increased intracranial pressure and toxic psychosis have also been reported in patients receiving quinolones, including ciprofloxacin.

Epileptic patients: Ciprofloxacin should be used with caution in epileptic patients and in patients who have suffered from previous CNS disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure or stroke). Ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible central-nervous side effects.

Effects on ability to drive: Even when taken as prescribed, this drug may cause dizziness and light headedness, and alter patients' responsiveness. It may therefore impair the ability to drive, operate machinery, or engage in activities requiring mental alertness or coordination. This is even more applicable when the drug is taken in conjunction with alcohol.

Myasthenia gravis: Ciprofloxacin might exacerbate symptoms of myasthenia gravis. Therefore, at any clinical sign or symptom of an exacerbation of myasthenia gravis, a physician should be consulted.

Tendon rupture: Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Therapy should be discontinued if the patient experiences pain, inflammation or rupture of a tendon.

Diabetes mellitus: Note that Aspen Ciprofloxacin Injection for Intravenous Infusion contains 55 mg/mL of glucose. The amount of glucose in the solution exceeds 100 mg per recommended daily dose. This may have a significant glycaemic effect on diabetes mellitus patients.

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

Elderly patients: Ciprofloxacin should be used with caution in the elderly after taking into account the severity of the illness and the creatinine clearance.

Impaired renal function: Alteration of the dosage regimen is necessary for patients with impairment of renal function (see **DOSAGE AND ADMINISTRATION**).

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

Effects on the liver: There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Interactions with other drugs

Theophylline: Concurrent administration of ciprofloxacin with theophylline may lead to elevated plasma concentrations of theophylline, prolongation of its elimination half life and increased adverse reactions, particularly those involving the CNS.

SERIOUS AND FATAL REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING CONCURRENT ADMINISTRATION OF CIPROFLOXACIN IV AND THEOPHYLLINE.

These reactions include cardiac arrest, convulsive seizures, status epilepticus and respiratory failure. Similar serious adverse events have been noted with administration of theophylline alone, however the possibility that ciprofloxacin may potentiate these reactions cannot be eliminated.

If concomitant use cannot be avoided, the plasma levels of theophylline should be monitored and appropriate dosage adjustments should be made.

Caffeine: Quinolones have also been shown to interfere with the metabolism of caffeine. It may reduce the clearance of caffeine and prolong its plasma half life. Patients are advised that ciprofloxacin may enhance the effects of caffeine.

Probenecid: Probenecid interferes with the renal excretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin results in a 50% reduction in the ciprofloxacin renal clearance, a 50% increase in AUC but without altering peak concentration or time to peak.

Cyclosporin: Some quinolones, including ciprofloxacin, have been associated with transient elevations of serum creatinine in patients receiving cyclosporin concomitantly.

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

Anticoagulants: Quinolones, including ciprofloxacin, have been reported to enhance the effects of oral anticoagulants, warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

NSAIDs: Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Use in pregnancy

Category B3

Reproduction studies have been performed in rats and mice at doses up to 100 mg/kg (0.6 and 0.3 times the maximum daily human dose based upon body surface area, respectively) and IV doses of up to 30 mg/kg and have revealed no evidence of impaired fertility or harm to the foetus due to ciprofloxacin. In rabbits, ciprofloxacin (30 and 100 mg/kg orally, 0.4 and 1.2 times the maximum daily human dose based upon body surface area, respectively) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion, intra-uterine deaths and foetal retardation, but no teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced in the rabbit, and no embryotoxicity or teratogenicity was observed.

There are, however, no adequate and well controlled studies in pregnant women. Like other drugs in its class, ciprofloxacin causes arthropathy in immature animals. Ciprofloxacin should be used in pregnancy only if the potential benefit justifies the potential risk to the foetus.

Australian categorisation definition of:

Category B3 - Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Use in lactation

Ciprofloxacin is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from ciprofloxacin, a decision should be made to discontinue nursing or to avoid using the drug, taking into account the importance of the drug to the mother.

Use in paediatrics

Ciprofloxacin is not recommended for use in pre-pubertal children, except for use in inhalational anthrax (post-exposure). Toxicological studies have shown that ciprofloxacin and related drugs such as nalidixic acid, norfloxacin and cinoxacin, can produce erosions of cartilage of weight bearing joints and other signs of arthropathy in immature animals of various species. Long term safety data, including effects on cartilage, following the administration of ciprofloxacin to paediatric patients are limited.

For the indication of inhalational anthrax (post-exposure), the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients is appropriate. For information regarding paediatric dosing in inhalational anthrax (post-exposure), see **DOSAGE AND ADMINISTRATION**. The safety and effectiveness of ciprofloxacin in pre-pubertal children except for use in inhalational anthrax (post-exposure) have not been established.

Carcinogenicity, mutagenicity, impairment of fertility

Ciprofloxacin was mutagenic in the mouse lymphoma assay and the rat primary hepatocyte culture/DNA repair assay *in vitro*, but not in other mammalian systems *in vitro* or in microbial systems.

In a small study on the chromosomal effects of ciprofloxacin on white blood cells, the drug did not exhibit any chromosomal abnormalities.

Carcinogenicity studies in mice (oral doses up to 1090 mg/kg/day and 1455 mg/kg/day in males and females, respectively; 1.4 and 1.8 times the highest recommended human dose of 1500 mg/day based upon body surface area) and rats (241 mg/kg/day and 328 mg/kg/day in males and females, respectively; 3.1 and 4.2 times the

highest recommended human dose of 1500 mg/day based upon body surface area) showed no evidence of carcinogenicity.

Results from photo co-carcinogenicity testing indicate that ciprofloxacin does not reduce the time to appearance of UV induced skin tumours as compared to vehicle control. Hairless (Skh-1) mice were exposed to UVA light for 3.5 hours five times every two weeks for up to 78 weeks while concurrently being administered ciprofloxacin. The time to development of the first skin tumours was 50 weeks in mice treated concomitantly with UVA and ciprofloxacin (mouse dose approximately equal to maximum recommended human dose based upon mg/m²), as opposed to 34 weeks when animals were treated with both UVA and vehicle. The times to development of skin tumours ranged from 16 to 32 weeks in mice treated concomitantly with UVA and other quinolones. In this model, mice treated with ciprofloxacin alone did not develop skin or systemic tumors. There are no data from similar models using pigmented mice and/or fully haired mice. The clinical significance of these findings to humans is unknown.

ADVERSE REACTIONS

Ciprofloxacin IV was generally well tolerated in the reported clinical trials at the recommended doses. Adverse events that were considered likely to be drug related occurred in 7.1% of courses, possibly related in 8.6%, and remotely related in 3.4%. The overall incidence of adverse reactions (29%) was higher than after oral ciprofloxacin (19%). Incidence increased progressively with increase in duration of treatment beyond 7 days.

The most frequently reported events, drug related or not, were nausea, diarrhoea, vomiting, rash, CNS disturbances, injection site reactions (e.g. oedema, hypersensitivity, inflammation, pain), abnormalities of liver enzymes and eosinophilia.

Additional events, drug related or not, that occurred in 1% or less of ciprofloxacin courses are listed below:

Gastrointestinal: mouth dryness, oral candidiasis, plaque on dentures, painful oral mucosa, dysphagia, anorexia, flatulence, constipation, vomiting, dyspepsia, epigastric pain, gastric irritation, ileus, jaundice, gastrointestinal bleeding, *C. difficile* associated diarrhoea, life threatening pseudomembranous colitis with possible fatal outcome, pancreatitis, hepatic necrosis, intestinal perforation.

Hepatic: allergic hepatitis, cholestatic jaundice, very rarely major liver disorders including hepatic necrosis.

CNS: hallucinations, confusion, convulsive seizures, nightmares, tremor, psychotic reaction (even progressing to self-endangering behaviour), depression, lethargy, drowsiness, somnolence, anxiety, nervousness, headache, dizziness, weakness, paraesthesia, dysphasia, manic reaction, sweating, unsteady gait, paranoia, ataxia, irritability, depersonalisation, insomnia, increase in intracranial pressure, peripheral paralgesia, hypoesthesia, hyperaesthesia, hypertonia, twitching.

Skin/hypersensitivity: erythema, burning, increased perspiration, urticaria, fever, photosensitivity reactions, angioedema, flushing, pruritus, chills, cutaneous candidiasis, anaphylactic reactions, erythema multiforme/Steven's-Johnson syndrome, exfoliative dermatitis, toxic epidermal necrolysis, vasculitis, hyperpigmentation, erythema nodosum, erythema multiforme exudativum (minor), papules, petechiae, Lyell syndrome, haemorrhagic bullae, serum-sickness like reaction, fixed eruption.

Ciprofloxacin has been shown to be phototoxic in a number of *in vitro* and *in vivo* studies. Nalidixic acid, the prototype quinolone antibiotic, produces photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to sunlight. Therapy should be discontinued if photosensitisation occurs.

Body as a whole: fatigue, malaise, aches, hot flushes, pain, pain in extremities, back pain, chest pain, injection site reaction (e.g. oedema/hypersensitivity/inflammation/pain).

Special senses: disturbed vision (blurred vision, colour vision, flashing lights, overbrightness of lights, diplopia), decreased visual acuity, retro-ocular pain, transient impairment of hearing especially at high frequencies, tinnitus, bad taste, impaired smell, loss of smell (usually reversible on discontinuation).

Respiratory: epistaxis, laryngeal oedema, wheezing, dyspnoea, hiccough, coughing, pulmonary embolism, respiratory arrest, respiratory distress, pleural effusion.

Metabolic or renal: interstitial nephritis, nephritis, renal failure, flare up of gout, acidosis, hyperglycaemia.

Urogenital: crystalluria, dysuria, polyuria, candiduria, vaginitis, haemorrhagic cystitis, urethral bleeding.

Cardiovascular: cardiovascular collapse, cardiopulmonary arrest, myocardial infarction, arrhythmia, tachycardia, cerebral thrombosis, palpitations, cardiac murmur, hypertension, hot flushes, migraine, syncope, hypotension, angina pectoris, thrombophlebitis (at infusion site).

Musculoskeletal: muscular pain, myasthenia, joint pain, joint swelling, tenosynovitis, tendovaginitis, tendinitis, predominantly affecting the achilles tendon, exacerbation of symptoms of myasthenia gravis. Achilles and other tendon ruptures that required surgical repair or resulted in prolonged disability have been reported with ciprofloxacin and other quinolones. Patients who are elderly or have had prior systemic treatment with corticosteroids are thought to be at particular risk. Therapy should be discontinued if the patient experiences pain, inflammation or rupture of a tendon.

Intravenous infusion site: burning, pain, erythema, swelling, paraesthesia, pruritus. Thrombophlebitis accounted for half the local reaction at the site of intravenous infusion, with the remainder being erythema, pruritus or burning pain. These reactions are more frequent with infusion time of 60 minutes or less. Most of these events which were described as only mild or moderate in severity, abated soon after the drug was discontinued, and required no treatment.

Other: In several instances nausea, vomiting, tremor, restlessness, agitation or palpitations were judged by investigators to be related to elevated plasma levels of theophylline possibly as a result of a drug interaction with ciprofloxacin.

Also reported were agranulocytosis, prolongation of prothrombin time and possible exacerbation of myasthenia gravis.

Adverse laboratory changes: Changes in laboratory parameters listed as adverse events without regard to drug relationship.

Hepatic: Elevations of AST (SGOT), ALT (SGPT), alkaline phosphatase, LDH, serum bilirubin.

Renal: Elevations of serum creatinine, serum urea, uric acid.

Urinalysis: Crystalluria, haematuria and albuminuria have been reported.

Haematologic: Eosinophilia, decreased blood platelets (thrombocytopenia), elevated blood platelets (thrombocytosis), decreased haemoglobin/ haematocrit, leukopenia, leukocytopenia, granulocytopenia.

Other: Elevations of serum creatinine, phosphokinase, elevations of serum theophylline (in patients receiving theophylline concomitantly), blood glucose, triglycerides.

Changes occurring in 0.1% or less of courses were: Decreased serum urea, elevated serum potassium, decreased serum potassium, decreased uric acid, elevated serum calcium, decreased total serum protein, elevated atypical lymphocyte count, decreased lymphocyte count, elevation of serum gamma-glutamyl transpeptidase (gamma-GT), decrease in platelet count, increase in blood monocytes, hyperglycaemia, immature WBCs, decreased serum albumin, cylindruria, elevated serum cholesterol.

Other changes occurring rarely during the administration of ciprofloxacin were elevation of serum amylase, increase in lipase, decrease in blood glucose, pancytopenia (life threatening), marrow depression (life threatening), leukocytosis, elevated sedimentation rate, elevation of serum phenytoin (in patients receiving phenytoin concomitantly), decreased prothrombin time, haemolytic anaemia and bleeding diathesis.

DOSAGE AND ADMINISTRATION

Aspen Ciprofloxacin Injection for Intravenous Infusion contains no antimicrobial preservative. Product is for single use in one patient only. Discard any residue.

Dosage

Intravenous therapy, for the indications mentioned below, should be used only when oral therapy is contraindicated. The usual dosage for adults is 200 to 300 mg every 12 hours. For complicated infections or for those caused by organisms not highly susceptible, 300 mg should be administered every 12 hours.

Dosage Guidelines				
Location of Infection	Type or Severity	Unit Dose	Daily Frequency	Total Daily Dose
Urinary tract	Severe/ Complicated	200 mg	q 12 h	400 mg
Lower respiratory tract infections (gram-negative)	Moderate	200 mg	q 12 h	400 mg
	Severe/ Complicated (less susceptible organisms)	300 mg	q 12 h	600 mg
Skin or skin structure	Severe/ Complicated (less susceptible organisms)	300 mg	q 12 h	600 mg
Blood				
Bone or joint	Adult	400 mg	q 12 h	800 mg
Inhalational Anthrax (post-exposure)*	Paediatric	10 mg/kg per dose, not to exceed 400 mg per dose	q 12 h	Not to exceed 800 mg

* Drug administration should begin as soon as possible after suspected or confirmed exposure. This indication is based on a surrogate endpoint, ciprofloxacin serum concentrations achieved in humans. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

Aspen Ciprofloxacin Injection for Intravenous Infusion should be administered only by intravenous infusion over a period of 60 minutes. Slow infusion of a dilute solution into a large vein will minimise patient discomfort and reduce the risk of venous irritation.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's host-defense mechanisms, and the status of renal and hepatic function.

The serum creatinine should represent a steady state of renal function.

Duration: The duration of treatment depends upon the severity of infection. Generally, ciprofloxacin should be continued for at least two days after the signs and symptoms of infection have disappeared. The usual duration is 7 to 14 days (parenteral therapy should be changed to oral ciprofloxacin tablets as soon as the condition warrants). In general, intravenous ciprofloxacin should not normally be given for greater than 14 days. However, for severe and complicated infections more prolonged therapy may be required. Total duration of ciprofloxacin administration (IV or oral) for inhalational anthrax (post-exposure) is 60 days.

In certain deep-seated infections involving abscess formation, appropriate surgical drainage should be performed in conjunction with antimicrobial therapy.

Impaired renal function: For creatinine clearance equal or less than 30 mL/min/1.73m², the maximum daily dose should be 400 mg/day for IV regimen.

When only data for serum creatinine are available, the following formula (Cockcroft's equation) may be used to estimate creatinine clearance.

$$\text{Men: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mmol/L)}} \times 0.0885$$

Women: 0.85 x the above value calculated for men.

Administration

Aspen Ciprofloxacin Injection for Intravenous Infusion solutions (0.2%) are available in 50 mL or 100 mL infusion bags.

The solution should be infused over a period of not less than 60 minutes by direct infusion or through a Y-type intravenous infusion set which may already be in place. If this method or the "piggyback" method of administration is used, it is advisable to discontinue temporarily the administration of any other solutions during the intravenous infusion of ciprofloxacin.

If Aspen Ciprofloxacin Injection for Intravenous Infusion is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each drug.

Compatibility and stability

Ciprofloxacin solutions are incompatible with all infusion solutions/drugs (e.g. penicillins, heparin solutions), which are physically or chemically unstable at the pH of ciprofloxacin (pH 3.5 to 4.6), especially when combined with alkaline solutions.

Since ciprofloxacin is slightly light sensitive, the solutions should be protected from light during storage.

OVERDOSAGE

In the event of acute overdosage, reversible renal toxicity has been reported in some cases. The patient should be carefully observed and given appropriate supportive treatment. Adequate hydration must be maintained. Only a small amount of ciprofloxacin (< 10%) is removed from the body after haemodialysis or peritoneal dialysis.

STORAGE

Store below 25°C. Protect from light.

PRESENTATION

Aspen Ciprofloxacin Injection for Intravenous Infusion is a clear, colourless, to slightly yellowish solution, available in infusion bags.

Strength

Aspen Ciprofloxacin Injection for Intravenous Infusion 100 mg/50 mL
Aspen Ciprofloxacin Injection for Intravenous Infusion 200 mg/100 mL

Pack Size

10 x 50 mL Bags
10 x 100 mL Bags

POISON SCHEDULE OF THE DRUG

All States and ACT - S4

NAME AND ADDRESS OF THE SPONSOR

Aspen Pharmacare Australia Pty Ltd
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