

CIPROFLO

Ciprofloxacin 2mg/ml Solution for IV infusion

Description

A colourless to slightly yellow clear sterile solution in glass vial.

Composition

Each ml contains 2mg of Ciprofloxacin.

Summary of pharmacodynamics and pharmacokinetics

Ciprofloxacin is a synthetic 4-quinolone derivative, with bactericidal activity. It acts via inhibition of bacterial DNA gyrase, ultimately resulting in interference with DNA function. Ciprofloxacin is highly active against a wide range of Gram-positive and Gram-negative organisms and has shown activity against some anaerobes, *Chlamydia* spp. and *Mycoplasma* spp.. Killing curves demonstrate the rapid bactericidal effect against sensitive organisms and it is often found that minimum bactericidal concentrations are in the range of minimum inhibitory concentrations. Ciprofloxacin has been shown to have no activity against *Treponema pallidum* and *Ureaplasma urealyticum*, *Nocardia asteroides*, and *Enterococcus faecium* are resistant.

Breakpoints

S $\leq$ 1 $\mu\text{g/ml}$, R $\geq$ 4 $\mu\text{g/ml}$

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local area information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

Plasmid-related transfer of resistance has not been observed with ciprofloxacin and the overall frequency of development of resistance is low (10^{-9} - 10^{-7}). Cross-resistance to penicillins, cephalosporins, aminoglycosides and tetracyclines has not been observed and organisms resistant to these antibiotics are generally sensitive to ciprofloxacin. Ciprofloxacin is also suitable for use in combination with these antibiotics, and additive behavior is usually observed.

Absorption of oral doses of ciprofloxacin 250mg, 500mg and 750mg tablet formulation occurs rapidly, mainly from the small intestine, the half-life of absorption being 2-15 minutes. Plasma levels are dose-related and peak 0.5-2.0 hours after oral dosing. The AUC also increases dose proportionately after administration of both single and repeated oral (tablet) and intravenous doses. The pharmacokinetic profile of intravenous ciprofloxacin was shown to be linear over the dose range (100mg-400mg). Following intravenous administration of ciprofloxacin, the mean maximum plasma concentrations were achieved at the end of the infusion period. That is, for a 100mg or 200mg dose, 30 minutes, and for a 400mg dose, 60 minutes. Reported plasma levels at this time point were 1.8mg/l, 3.4mg/l and 3.9mg/l, respectively. The absolute bioavailability is reported to be 52-83% and ciprofloxacin is subject to only slight first-pass metabolism.

Distribution of ciprofloxacin within tissues is wide and the volume of distribution high, though slightly lower in the elderly. Protein binding is low (between 19-40%). Ciprofloxacin is present in plasma largely in a non-ionised form.

Only 10-20% of a single oral or intravenous dose is eliminated as metabolites (which exhibit lower activity than the parent drug). Four different antimicrobially active metabolites have been reported, desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxaciprofloxacin (M3) and

formylciprofloxacin (M4). M2 and M3 account for one third each of metabolised substance and M1 is found in small amounts (1.3-2.6% of the dose). M4 has been found in very small quantities (<0.1% of the dose). M1-M3 have antimicrobial activity comparable to nalidixic acid and M4 found in the smallest quantity has antimicrobial activity similar to that of norfloxacin.

Elimination of ciprofloxacin and its metabolites occurs rapidly, primarily by the kidney. After single oral and intravenous doses of ciprofloxacin, 55% and 75% respectively are eliminated by the kidney and 39% and 14% in the faeces within 5 days. Renal elimination takes place mainly during the first 12 hours after dosing and renal clearance levels suggest that active secretion by the renal tubules occurs in addition to normal glomerular filtration. Renal clearance is between 0.18-0.3 l/h.kg and total body clearance between 0.48-0.60 l/h.kg. The elimination kinetics are linear and after repeated dosing at 12 hourly intervals, no further accumulation is detected after the distribution equilibrium is attained (at 4-5 half-lives). The elimination half-life of unchanged ciprofloxacin over a period of 24-48 hours post-dose is 3.1-5.1 hours. A total body clearance of approximately 35l/h was observed after intravenous administration.

Some studies carried out with ciprofloxacin in severely renally impaired patients (serum creatinine >265 micromole/l or creatinine clearance <20ml/minute) demonstrated either a doubling of the elimination half-life, or fluctuations in half-life in comparison with healthy volunteers, whereas other studies showed no significant correlation between elimination half-life and creatinine clearance. However, it is recommended that in severely renally impaired patients, the total daily dose should be reduced by half, although monitoring of drug serum levels provides the most reliable basis for dose adjustment as necessary.

Results of pharmacokinetic studies in paediatric cystic fibrosis patients have shown dosages of 20mg/kg orally twice daily or 10mg/kg iv three times daily are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimen.

Indications

Ciproflo 2mg/ml Solution for Infusion is indicated in the treatments of wide range of infections including anthrax, biliary tract infections, infected bites and stings, bone and joint infections, cat scratch disease, chancroid, exacerbations of cystic fibrosis, gastro-enteritis (traveller's diarrhoea and campylobacter enteritis, cholera, salmonella enteritis, shigellosis), gonorrhoea, neutropenia, legionnaires's disease, otitis externa, otitis media, peritonitis, Q fever, lower respiratory-tract infections (pseudomonal infections in cystic fibrosis) septicaemia, skin infections (soft-tissue infections), spotted fevers, typhoid and paratyphoid fever, typhus, and urinary-tract infections. Used also as a prophylaxis for meningococcal meningitis and surgical infections.

Adverse reactions/side effects

Ciprofloxacin is generally well tolerated. Gastrointestinal disturbances include nausea, vomiting, diarrhoea, abdominal pain, and dyspepsia are the most frequent side effects. Pseudomembranous colitis has been reported rarely. The most common on the CNS are headache, dizziness, restlessness, drowsiness, insomnia, nightmares and other sensory disturbances. More rarely, hallucinations, psychotic reactions, depression, and convulsions. Rash, pruritus, hypersensitivity-type reactions have been included, rarely, vasculitis, erythema multiforme, Stevens-Johnsons syndrome, and toxic epidermal necrolysis. Anaphylaxis, transient increase in serum creatinine or blood urea nitrogen and occasionally acute renal failure, interstitial nephritis; crystalluria; elevated liver enzyme values, jaundice and hepatitis; haematological disturbances including eosinophilia, leucopenia, thrombocytopenia and very rarely, pancytopenia, haemolytic anemia, or agranulocytosis; myalgia; gynaecomastia and cardiovascular effects like, tachycardia, oedema, syncope, hot flushes and sweating. Pain and irritation may occur at the site of injection accompanied rarely by phlebitis or thrombophlebitis.

Precautions/warnings

Ciprofloxacin should be used with caution in patients with epilepsy or a history of CNS disorders. Should not be used in children, adolescents. Pregnant women, or breastfeeding mothers or use only if the benefits outweighs the risks.

Contraindications

Ciproflo is contraindicated to some patients who experience tendon pain, inflammation or rupture and the treatment should be discontinued to prevent tendon damage.

Dosage and directions for use

Ciproflo 2mg/ml Solution infusions may be administered by intravenous infusion.

Adult:

100 to 400 mg twice daily, given over 30 to 60 minutes as a solution containing the equivalent of 1-2 mg/mL.

Children:

4 to 8 mg/kg twice daily is suggested.

10 mg/kg twice daily up to maximum of 400 mg twice daily (for exacerbation of cystic fibrosis associated with *Pseudomonas aeruginosa* infection)

Incompatibility

Ciprofloxacin is incompatible with aminophylline, amoxicillin, cefepime, clindamycin, dexamethasone, floxacillin, furosemide, heparin and phenytoin. If ciprofloxacin is to be given concurrently with another medication, each medication should be administered separately. The injection should be freshly prepared and unused portions should be discarded.

Use in pregnancy and lactation

Reproduction studies performed in mice, rats and rabbits using parenteral and oral administration did not reveal any evidence of teratogenicity, impairment of fertility or impairment of peri-/post-natal development. However, as with other quinolones, ciprofloxacin has been shown to cause arthropathy in immature animals, and therefore its use during pregnancy is not recommended. Studies have indicated that ciprofloxacin is secreted in breast milk. Administration to nursing mothers is thus not recommended.

Drug interactions

Aluminum, magnesium or iron reduces absorption of Ciprofloxacin. It also decreases the clearance of theophylline, increases blood concentrations of midazolam according to some isolated reports. The urinary excretion of Ciprofloxacin is reduced by probenecid. When used simultaneously with azlocillin, it has resulted in higher and more prolonged concentration of Ciprofloxacin. Changes in the pharmacokinetics of fluoroquinolones such as Ciprofloxacin have been reported when given with histamine H₂ antagonists, possibly due to the change in gastric pH, but do not seem to be of much of clinical significance.

Theophylline, interferes with metabolism of caffeine, enhances effects of oral anticoagulants warfarin, glibenclamide, probenecid, metoclopramide and its derivatives.

Overdosage, symptoms and treatment

Based on the limited information available in two cases of ingestion of over 18g of ciprofloxacin, reversible renal toxicity has occurred. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients must be kept well hydrated, and in the case of renal damage resulting in prolonged oliguria, dialysis should be initiated.

Serum levels of ciprofloxacin are reduced by dialysis.

Presentation

This infusion is available in 50ml bottle (100mg solution for infusion) and 100ml bottle (200mg solution for infusion).

One bottle are packed into one paper box.

Storage conditions

Protect from light and store below 30°Celsius. Keep out of reach of children.

Shelf-life

The injections can be used within 36 months from the date of manufacture if kept as recommended.

Registration number

CIPROFLO MAL 200XXXXXA

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