

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Truoxin 750 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ciprofloxacin 750 mg as the hydrochloride.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White or yellowish, 10 x 19mm oblong, biconvex film-coated tablets. Scored on one side and side wall scored, marked C750 on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Ciprofloxacin is indicated for the treatment of infections caused by sensitive bacteria:

Upper and lower respiratory tract infections: For example broncho- and lobar-pneumonia, bronchitis (acute and chronic), acute exacerbation of cystic fibrosis, bronchiectasis, empyema, Gram-negative pneumonia (but *not* first-line therapy for pneumococcal pneumonia).

Urinary tract infections: For example urethritis (complicated and uncomplicated), cystitis, pyelonephritis, prostatitis, epididymitis.

Gastro-intestinal infections: For example enteric fever, infective diarrhoea.

Gonorrhoea: For example urethral, rectal and pharyngeal gonorrhoea caused by beta-lactamase producing organisms or bacteria moderately sensitive to penicillin.

4.2 Posology and method of administration

Dosage is determined by the type and severity of infection, sensitivity of the causal organism(s) and the age, weight and renal function status of the patient.

Truoxin Tablets should be swallowed whole with an adequate amount of liquid. If Truoxin Tablets are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, the tablets should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt, calcium and fortified orange juice). However, a normal diet that will contain small amounts of calcium, does not significantly affect ciprofloxacin absorption.

Adults:

The normal treatment dosage range is between 100mg and 750mg twice a day.

Lower and upper respiratory tract infections:

250mg to 750mg twice a day, depending on severity. Ciprofloxacin is not recommended as an initial treatment of pneumococcal pneumonia, however where its use is appropriate, the dose is 750mg twice a day. Usual duration of treatment: 7 – 14 days.

Pseudomonas infections in patients with cystic fibrosis: normal dose 750mg twice a day. The low body mass of these patients must be considered when determining dosage.

Urinary tract infections:

Acute, uncomplicated cystitis in women: 100mg twice a day for 3 days.

Prostatitis: 500mg twice daily, up to 28 days.

Complicated infections and pyelonephritis: 250mg to 500mg twice daily. Usual duration of treatment 7 –14 days.

Other urinary tract infections: 250mg to 500mg twice a day.

Gastrointestinal infections:

500mg twice daily, usual duration of treatment 3 – 7 days.

Gonorrhoea:

One dose of 250mg only.

Other infections:

500mg to 750mg twice a day. In severe infections (especially due to pseudomonas, staphylococci and streptococci), 750mg twice a day.

Elderly:

Although higher ciprofloxacin serum levels are found in the elderly, no adjustment of dosage is necessary.

Patients with impaired renal function:

Dosage adjustments are not usually required, except in patients with severe renal impairment, i.e. serum creatinine >265 micromol/l or creatinine clearance of <20ml/minute. If adjustment is necessary, this may be achieved by reducing the total daily dose by half, although monitoring of drug serum levels provides the most reliable basis for dose adjustment.

Dialysis reduces serum levels of ciprofloxacin.

Children and adolescents:

As with other drugs in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Although analysis of available safety data from ciprofloxacin use in patients is less than 18 years of age, the majority of whom had cystic fibrosis, did not disclose any evidence of drug-related cartilage or articular damage, its use in the paediatric population is generally not recommended.

Clinical and pharmacokinetic data support the use of ciprofloxacin in paediatric cystic fibrosis patients (ages 5-17 years) with acute pulmonary exacerbation associated with *P. aeruginosa* infection, at a dose of 20mg/kg orally twice daily (maximum daily dose 1500mg).

For indications other than treatment of pulmonary exacerbations in cystic fibrosis ciprofloxacin may be used in children and adolescents where the benefit is considered to outweigh the potential risks.

Dosing in children with impaired renal and/or hepatic function has not been studied.

Duration of treatment:

The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings.

In acute, uncomplicated cystitis the treatment period is three days with Truoxin 100mg Film-coated Tablets or Truoxin 250mg Film-coated Tablets.

In other acute infections the usual treatment period is 5 to 10 days with Truoxin Tablets. Generally, treatment should be continued for at least three days after the signs and symptoms of the infection have disappeared.

Prolonged treatment or use in chronic conditions should only be initiated under consultant direction with regular surveillance.

For acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients (aged 5-17 years), the duration of treatment is 10-14 days.

4.3 Contraindications

Ciprofloxacin is contra-indicated:

- If patients are sensitive to ciprofloxacin, quinolone antibiotics, or any of the excipients, or other quinolone anti-infectives
- In children and growing adolescents unless epiphyseal closures of long bones have occurred or where the benefits of treatment outweigh the risks.
- In patients with a history of quinolone-induced tendon disorder.

Concurrent administration of ciprofloxacin and tizanidine is contraindicated since an undesirable increase in serum tizanidine concentrations associated with clinically relevant tizanidine-induced side-effects (hypotension, somnolence) can occur.

4.4 Special warnings and precautions for use

In the event of hypersensitivity, which in some instances can occur after the first administration, therapy should be discontinued.

Ciprofloxacin should be used with caution in epileptics and patients with existing central nervous system disorders or a history of convulsive disorders and only if the benefits of treatment are considered to outweigh the risk of possible CNS side-effects. CNS side-effects have been reported after first administration of ciprofloxacin in some patients. Treatment should be discontinued if the side-effects, depression or psychoses lead to self-endangering behaviour (see also Section 4.8, Undesirable effects).

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

Patients with a family history of or actual defects in glucose-6-phosphate dehydrogenase activity are prone to haemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.

Ciprofloxacin is not recommended as first-line therapy for the treatment of pneumococcal pneumonia. *Streptococcus pneumoniae* is the most frequent pathogen responsible for community acquired pneumonia.

Tendon inflammation and rupture may occur with quinolone antibiotics. Such reactions have been observed particularly in older patients and in those treated concurrently with corticosteroids. At first signs of pain or inflammation, patients should discontinue ciprofloxacin and rest the affected limbs.

Toxicological studies have shown that administration of oxyquinolone antibacterial agents at doses higher than the therapeutic range can produce erosion of the cartilage in weight-bearing joints in immature animals of some species. No such lesions have been shown to occur in man to date. This product should not be prescribed for children or those in whom bone growth is continuing, with the exception of paediatric cystic fibrosis patients or for the treatment of inhalation anthrax, unless the benefit of short-term use is regarded as exceeding the risk.

Patients with pre-existent significant renal or hepatic disorders should be carefully monitored to detect any deterioration in function. It should only be administered with great caution to persons with renal insufficiency, or severe dehydration. There is a risk of pseudomembranous colitis with broad-spectrum antibiotics possibly leading to a fatal outcome. It is important to consider this in patients suffering from severe, persistent diarrhoea. With ciprofloxacin this effect has been reported rarely. If pseudomembranous colitis is suspected treatment with ciprofloxacin should be stopped and appropriate treatment given (e.g. oral vancomycin). Drugs that inhibit peristalsis must not be given.

Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e., sunburn-like skin reactions) occur.

Laboratory tests may give abnormal findings if performed whilst patients are receiving ciprofloxacin e.g. increased alkaline phosphatase; increases in liver function tests e.g. transaminases and cholestatic jaundice, especially in patients with previous liver damage.

Eradication of infection due to *Pseudomonas* in persons with cystic fibrosis only occurs in a minority of cases, particularly after repeat courses of treatment with ciprofloxacin. Cyclical or alternating antibacterial therapies may help reduce the number of resistant strains.

4.5 Interaction with other medicinal products and other forms of interaction

Increased plasma levels of theophylline have been observed following concurrent administration with ciprofloxacin. It is recommended that the dose of theophylline should be reduced and plasma levels of theophylline monitored. The reaction between theophylline and ciprofloxacin is potentially life threatening. Therefore, when monitoring of plasma levels is not possible, the use of ciprofloxacin should be avoided in patients receiving theophylline. Particular caution is advised in those patients with convulsive disorders.

Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, tacrine, ropinirole, tizanidine, duloxetine).

Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations, especially of theophylline, may be necessary.

In a crossover study, 10 healthy subjects were given ciprofloxacin 500mg or placebo twice daily for three days, at the end of which a single dose of tizanidine 4 mg was given. There was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin compared to placebo. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine must not be administered together with ciprofloxacin (refer to Section 4.3, Contraindications).

In clinical studies it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and C_{max} of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration. Phenytoin levels may be altered when Ciproxin is used concomitantly.

Ciproxin Tablets should not be administered within four hours of multivalent cationic drugs and mineral supplements (e.g. calcium, magnesium, aluminium or iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids and highly buffered drugs (e.g. anti retrovirals) as interference with absorption may occur. When appropriate, patients should be advised not to self-medicate with preparations containing these compounds during therapy with ciprofloxacin. This restriction does not apply to the class of H₂ receptor blocker drugs.

The concurrent administration of dairy products or fortified drinks alone (e.g. milk, yoghurt, calcium, fortified orange juice) and ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. However a normal diet, that will contain small amounts of calcium, does not significantly affect ciprofloxacin absorption.

Prolongation of clotting time has been reported during concomitant administration of ciprofloxacin and oral anti-coagulants.

Ciprofloxacin may interfere with estimations of urinary 17-ketosteroids, or vanillylmandelic acid.

Animal data have shown that high doses of quinolones in combination with some non-steroidal anti-inflammatory drugs, (e.g. fenbufen, but not acetylsalicylic acid) can lead to convulsions.

Transient increases in serum creatinine have been seen following concomitant administration of ciprofloxacin and ciclosporin. Therefore, monitoring of serum creatinine levels is advisable.

Concomitant use with some phenylpropionic acid-derived non-steroidal anti-inflammatory drugs may lead to toxicity possibly because of renal effects. The simultaneous administration of quinolones and glibenclamide resulting in hypoglycaemia. Renal tubular transport methotrexate may be inhibited by concomitant methotrexate. This may increase the risk of methotrexate associated with toxic reactions. Therefore, patients receiving methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

Concomitant use with probenecid reduces the renal clearance of ciprofloxacin, resulting in increased quinolone plasma levels.

The use of metoclopramide with ciprofloxacin may accelerate the absorption of ciprofloxacin.

4.6 Fertility, pregnancy and lactation

Ciprofloxacin should not be used during pregnancy, or in women at risk of pregnancy nor during 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 or in women capable of childbearing is not recommended. Studies have indicated that ciprofloxacin is secreted in breast milk. Administration to nursing mothers is thus not recommended.

4.7 Effects on ability to drive and use machines

Ciprofloxacin could result in impairment of the patient’s ability to drive or operate machinery, particularly in conjunction with alcohol.

4.8 Undesirable effects

Adverse drug reactions based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency using MedDRA terminology are listed below.
The most frequently reported adverse reactions are nausea, diarrhoea and injection and infusion site reactions (intravenous administration only).
Adverse drug reactions derived from post-marketing reports are included in the column frequency “not known”.

Common ≥1% to <10%	Uncommon ≥0.1% to <1%	Rare ≥0.01% to <0.1%	Very rare <0.01%	Not known
Infections and Infestations				
	Candida infections	Antibiotic associated colitis (<i>very rarely associated with possible fatal outcome, see section 4.4, Special warnings and precautions for use</i>)		
Blood and Lymphatic System Disorders				
	Eosinophilia	Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocythaemia	Haemolitic anaemia, Agranulocytosis, Pancytopenia (life-threatening)	
Immune System Disorders				
		Allergic reactions, Allergic oedema / angiooedema	Anaphylactic reactions, Anaphylactic shock (<i>life-threatening</i>)	Serum sickness-like reaction
Metabolism and Nutrition Disorders				
	Anorexia	Hyperglycaemia		
Psychiatric Disorders				
	Psychomotor hyperactivity / agitation	Confusion and disorientation, Anxiety reaction	Psychotic reactions (which may progress to self-endangering behaviour)	
Nervous System Disorders				
	Headache, Dizziness, Sleep disorders, Taste disorders (<i>usually reversible upon discontinuation of treatment</i>)	Par- and Dys-aesthesia, Hypoaesthesia, Tremor, Seizures, Vertigo, Somnolence	Migraine, Disturbed coordination, Smell disorders	Hyperaesthesia Intracranial hypertension

Eye Disorders				
		Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders				
		Tinnitus, Hearing loss	Hearing impaired	
Cardiac Disorders				
		Tachycardia		
Vascular Disorders				
		Vasodilation, Hypotension, Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders				
		Dyspnoea (<i>including asthmatic condition</i>)		
Gastrointestinal Disorders				
Nausea Diarrhoea	Vomiting Gastronintestinal and abdominal pain Dyspepsia Flatulence	Dysphagia	Pancreatitis	
Hepato-biliary Disorders				
	Transient increase in transaminases Increased bilirubin	Transient hepatic impairment Jaundice Hepatitis (<i>non infective</i>)	Liver necrosis (<i>very rarely progressing to life- threatening hepatic failure</i>)	
Skin and Subcutaneous Tissue Disorders				
	Rash Pruritus Urticaria	Photosensitivity reactions Unspecific blistering	Petechiae Erythema multiforme minor	Erythema nodosum Stenves-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal, Connective Tissue and Bone Sidorders				
	Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (<i>predominantly Achilles tendon, see section 4.4, Special warnings and precautions for use</i>)	Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders				
	Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis		

General Disorders and Administration Site Conditions				
	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)		Gait disturbance
Investigations				
	Transient increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		

4.9 Overdose

Based on the limited information available in two cases of ingestion 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. Calcium or magnesium antacids may be administered as soon as possible after ingestion of Cirpoxin Tablets in order to reduce the absorption of ciprofloxacin. Serum levels of ciprofloxacin are reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Therapeutic classification: J 01 MA 02

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.

Spectrum of activity:

Breakpoints:

BSAC*: S ≤ 1 mg/L; R ≥ 2 mg/L, except *Pseudomonas* R ≥ 8 mg/L and UTI R ≥ 8 mg/L.

NCCLS**: S ≤ 1 mg/L; I = 1 to 2 mg/L; R ≥ 4 mg/L.

* British Society for Antimicrobial Chemotherapy

Susceptibility:

The prevalence of the acquired resistances can vary for some species geographically and with time. Therefore, it is important to obtain information on local resistance patterns, particularly when treating more severe infections. The information provided below gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

Organism	Prevalence of Resistance %
Sensitive:	
Gram-positive bacteria	
<i>Corynebacterium diphtheriae</i>	0
<i>Corynebacterium</i> spp.	N/A
<i>Staphylococcus aureus</i> (methicillin sensitive)	0 – 14
<i>Staphylococcus aureus</i> (methicillin resistant)	48 – 90
<i>Streptococcus agalactiae</i>	0 – 17

Gram-negative bacteria	
<i>Acinetobacter buamanii</i>	6 – 93
<i>Acinetobacter spp.</i>	14 – 70
<i>Aeromonas hydrophilia</i>	0
<i>Aeormonas spp.</i>	N/A
<i>Bordetella pertussis</i>	0
<i>Brucella melitensis</i>	0
<i>Campylobacter jejuni/coli</i>	0 – 82
<i>Campylobacter spp.</i>	0
<i>Citrobacter freundii</i>	0 – 4
<i>Citrobacter spp.</i>	0
<i>Edwardsiella tarda</i>	0
<i>Enterobacter aerogenes</i>	0
<i>Eneterobacter cloacae</i>	0 – 3
<i>Eneterobacter spp.</i>	3 – 13
<i>Escherichia coli</i>	2 – 7
<i>Escherichia coli, EHEC and EPEC</i>	N/A
<i>Haemophilus influenzae</i>	0 – 1
<i>Haemophilus influenzae</i> (β -lactam negative)	0
<i>Haemophilus influenzae</i> (β -lactam positive)	0
<i>Haemophilus parainfluenzae</i>	0
<i>Hafnia alvei</i>	0
<i>Klebsiella oxytoca</i>	0
<i>Klebsiella pneumoniae</i>	2 – 5.8
<i>Klebsiella spp.</i>	2 – 21
<i>Legionella pneumonophilia</i>	0
<i>Legionella spp.</i>	0
<i>Moraxella catarrhalis</i>	0
<i>Morganella morganii</i>	1 – 2
<i>Neisseria gonorrhoeae</i>	0
<i>Neisseria gonorrhoeae, β-lactamase</i>	0
<i>Neisseria gonorrhoeae, β-lacatamse positive</i>	0
<i>Neisseria meningitidis</i>	0
<i>Neisseria meningitidis, β-lactamase negative</i>	0
<i>Plesiomonas shigelloides</i>	0
<i>Proteus mirabilis</i>	0 – 10
<i>Proteus vulgaris</i>	4
<i>Providencia rettgeri</i>	N/A
<i>Providencia spp.</i>	4
<i>Providencia stuartii</i>	N/A
<i>Pseudomonas aeruginosa</i>	1 – 28
<i>Salmonella spp.</i>	0
<i>Salmonella typhi</i>	0 – 2
<i>Serratia liquefaciens</i>	N/A
<i>Serratia marcescens</i>	23
<i>Serratia spp.</i>	0 – 21
<i>Shigella spp.</i>	0
<i>Vibrio cholerae</i>	0
<i>Vibrio parahaemolyticus</i>	0
<i>Vibrio spp.</i>	0

<i>Yersinia enterocolitica</i>	0
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Anaerobes	
<i>Bacteroides ureolyticus</i>	0
<i>Clostridium perfringens</i>	N/A
<i>Peptococcus spp.</i>	0
<i>Peptostreptococcus spp.</i>	N/A
<i>Peptostreptococcus magnus</i>	0
<i>Veillonella parvula</i>	0
Other pathogens	
<i>Chlamydia spp.</i>	N/A
<i>Helicobacter pylori</i>	N/A
<i>Mycobacterium fortuitum</i>	0
<i>Mycobacterium tuberculosis</i>	0
<i>Mycoplasma hominis</i>	16
Intermediate	
Gram-positive aerobes	
<i>Enterococci</i>	5
<i>Enterococcus faecalis</i>	9 – 34
<i>Staphylococcus epidermis, methicillin sensitive</i>	10 – 16
<i>Staphylococcus epidermis, methicillin resistant</i>	26 – 56
<i>Staphylococcus haemolyticus</i>	N/A
<i>Staphylococcus haemolyticus, methicillin sensitive</i>	8
<i>Staphylococcus haemolyticus, methicillin resistant</i>	73
<i>Streptococcus anginosus</i>	9
<i>Streptococcus bovis</i>	N/A
<i>Streptococcus milleri</i>	5
<i>Streptococcus mitis</i>	N/A
<i>Streptococcus pneumoniae, penicillin sensitive</i>	0 – 1
<i>Streptococcus pneumoniae, penicillin intermediate</i>	N/A
<i>Streptococcus pneumoniae, penicillin intermediate and resistant</i>	2.8
<i>Streptococcus pneumoniae, penicillin resistant</i>	N/A
<i>Streptococcus pyogenes</i>	0 – 28
<i>Streptococcus viridans group</i>	N/A
<i>Streptococcus viridans, penicillin sensitive</i>	N/A
<i>Streptococcus viridans, penicillin resistant</i>	N/A
<i>Streptococcus, β-haemolytic groups A, C, and G</i>	0
Gram-negative aerobes	
<i>Alcaligenes spp.</i>	N/A
<i>Listeria monocytogenes</i>	0
<i>Listeria spp.</i>	0
Anaerobes	
<i>Fusobacterium spp.</i>	N/A
<i>Gardnerella vaginalis</i>	0
<i>Prevotella spp.</i>	N/A
Other pathogens	
<i>Ureaplasma urealyticum</i>	11
Resistant	
Gram-positive aerobes	
<i>Enterococcus faecium</i>	N/A

<i>Stenotrophomonas maltophilia</i>	94
<i>Streptococcus sanguis</i>	N/A

Gram-negative aerobes	
<i>Flavobacterium meningosepticum</i>	N/A
<i>Nocardia asteroides</i>	N/A
Anaerobes	
<i>Bacteroides fragilis</i>	N/A
<i>Bacteroides thetaiotaomicron</i>	N/A
<i>Clostridium difficile</i>	N/A

* Ciprofloxacin is not considered the drug of first choice for treatment of infections with anaerobes. In-vitro investigations have shown that resistance to ciprofloxacin is commonly due to mutations in bacterial topoisomerases and usually develops slowly and gradually (“multiple-step” type).

Resistance

Plasmid-related transfer of resistance has not been observed with ciprofloxacin and the overall frequency of development of resistance is low (10^{-19} - 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 behaviour is usually observed.

5.2 Pharmacokinetic properties

Absorption of oral doses of ciprofloxacin 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 0.2-2.0 hours after dosing. The AUC also increases proportionately after administration of both single and repeated oral (tablet) and intravenous doses. Plasma levels peak approximately 1.5-2.5 hours after dosing and the $AUC_{0-\infty}$ is in the range of 5-12mg.h/l. The absolute bioavailability is reported to be 52-83% and ciprofloxacin is subject to only slight first pass metabolism. The oral bioavailability is approximately 70-80%. The intake of food at the same time as administration of oral ciprofloxacin has a marginal but clinically not relevant effect on the pharmacokinetic parameters C_{max} and AUC. No specific recommendations are necessary with regard to time of administration of oral ciprofloxacin relative to food intake. 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%).

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. Approximately 1% of ciprofloxacin dose is excreted via the biliary route. 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.

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 time daily are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimen.

Inhalation anthrax: Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for the recommended doses.

5.3 Preclinical safety data

Following extensive oral and intravenous toxicology testing with ciprofloxacin, only two findings which may be considered relevant to the use of ciprofloxacin in man were observed. Crystalluria was noted in those species of animals which had a normally alkaline urine. Kidney damage without the presence of crystalluria was not observed. This effect is considered a secondary inflammatory foreign-body reaction. Due to the precipitation of a crystalline complex of ciprofloxacin, magnesium and protein in the distal tubule system of the kidneys. This is considered not to be a problem in man, because the urine is normally acidic. However, to avoid the occurrence of crystaluria, patients should be well hydrated and excessive alkalinity of the urine avoided.

As with other quinolones, damage to the weight-bearing joints of only juvenile rates and dogs treated with ciprofloxacin was noted in repeat dose toxicity testing. This was more noticeable in the dog. Although the relevance of this to man is unknown, the use of ciprofloxacin in children and growing adolescents is not recommended (with the exception of treatment of cystic fibrosis and inhalation anthrax), unless the benefits are considered to outweigh the potential risks.

Additionally, because of the potential of arthropathy, the use of ciprofloxacin during pregnancy, in women capable of child bearing and in nursing mothers is not recommended.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Crospovidone (type B)
Colloidal anhydrous silica
Magnesium stearate
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister strips of 20 µm Aluminium and 250 µm PVC in a cardboard outer container. Pack size: 6, 7, 10, 14, 28, 30, 56, 60, 84, 90, 100, 120, 150 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Sinclair IS Pharma Ireland Limited
Damastown
Mulhuddart
Dublin 15

8 MARKETING AUTHORISATION NUMBER

PA0915/010/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 03/12/2001

Date of last renewal: 03/12/2006

10 DATE OF REVISION OF THE TEXT

April 2012