SUMMARY OF PRODUCT CHARACTERISTICS

1. TRADE NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 500 mg, film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 582.0mg ciprofloxacin hydrochloride equivalent to 500mg ciprofloxacin (INN).

For excipients see 6.1

3. PHARMACEUTICAL FORM

Film coated tablets.

Off-white,capsule shaped, biconvex, film coated tablets with CP/500 on one side and ⓚ on the other.

4.1 Therapeutic indications

Because of the risk of prolonged, disabling and potentially irreversible serious adverse drug reactions (see section 4.4 and section 4.8) this product must only be prescribed when other antibiotics that are commonly recommended for the infection are inappropriate. This applies to all indications listed below. Situations where other antibiotics are considered to be inappropriate are where:

- there is resistance to other first-line antibiotics recommended for the infection;
- other first-line antibiotics are contraindicated in an individual patient;
- other first-line antibiotics have caused side effects requiring treatment to be stopped;

treatment with other first-line antibiotics has failed.

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

Adults:

Respiratory tract infections: e.g. lobar and bronchopneumonia, acute and chronic bronchitis, acute exacerbation of cystic fibrosis, bronchiectasis, empyema. Ciprofloxacin is not recommended as first-line therapy for the treatment of pneumococcal pneumonia. Ciprofloxacin may be used for treating Gram-negative pneumonia.

Ear, nose and throat infections: e.g. mastoiditis, otitis media and sinusitis, especially if due to Gram-negative bacteria (including *Pseudomonas* spp.).

Ciprofloxacin is not recommended for the treatment of acute tonsillitis.

Eye infections: e.g. bacterial conjunctivitis.

Urinary tract infections: e.g. uncomplicated and complicated urethritis, cystitis, pyelonephritis, prostatitis, epididymitis.

Skin and soft tissue infections: e.g. infected ulcers, wound infections, abscesses, cellulitis, otitis externa, erysipelas, infected burns.

Bone and joint infections: e.g. osteomyelitis, septic arthritis.

Intra-abdominal infections: e.g. peritonitis, intra-abdominal abscesses.

Infections of the biliary tract: e.g. cholangitis, cholecystitis, empyema of the gall bladder.

Gastro-intestinal infections: e.g. enteric fever, infective diarrhoea.

Pelvic infections: e.g. salpingitis, endometritis, pelvic inflammatory disease.

Severe systemic infections: e.g. septicaemia, bacteraemia, peritonitis, infections in immuno-suppressed patients.

Gonorrhoea: including urethral, rectal and pharyngeal gonorrhoea caused by ß-lactamase producing organisms or organisms moderately sensitive to penicillin.

Ciprofloxacin is also indicated for prophylaxis against infection in elective upper gastro-intestinal tract surgery and endoscopic procedures, where there is an increased risk of infection.

Children:

For the treatment of acute pulmonary exacerbation of cystic fibrosis associated with *P. aeruginosa* infection in paediatric patients aged 5-17 years.

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

4.2 Posology and Method of Administration

General dosage recommendations: The dosage of Ciprofloxacin film coated tablets is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, weight and renal function of the patient. Ciprofloxacin film coated tablets should be swallowed whole with an adequate amount of liquid.

Adults

The dosage range for adults is 250-750mg twice daily. The following dosages for specific types of infection are recommended:

Table 1 : Recommended Adult Dosage

Indication	Dosage (mg ciprofloxacin)
Treatment	
Gonorrhoea	250mg single dose
Upper and lower urinary tract infections (depending on severity)	250-500mg b.d.
Upper and lower respiratory tract infections (depending on severity) Pneumococcal pneumonia (second-line)	250-750mg b.d. 750mg b.d.
Cystic fibrosis patients with pseudomonal lower RTI*	750mg b.d.
Other infections as detailed under 4.1	500-750mg b.d.
Severe infections, particularly due to Pseudomonas, staphylococci and streptococci	750mg b.d.
Prophylaxis	
Elective upper gastro-intestinal surgical and endoscopic procedures	750mg single dose 60-90 minutes prior to the procedure**. If gastro-oesophageal obstructive lesions are suspected use with an anti-infective effective against anaerobes

* Although the pharmacokinetics of ciprofloxacin remains unchanged in patients with cystic fibrosis, the low bodyweight of these patients should be taken into consideration when determining dosage.
** The tablet may be given with an oral pre-medicant, but see Section 4.5

Impaired Renal Function

Dosage adjustments are not usually required, except in patients with severe renal impairment (serum creatinine >265 micromole/l or creatinine clearance <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.

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

Adolescents and children
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 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 (aged 5 - 17 years) with acute pulmonary exacerbations 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. In these cases a dosage of 5-15mg/kg orally twice daily should be administered depending upon the severity of infection.

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.

In other acute infections the usual treatment period is 5-10 days. Generally, acute and chronic infections (e.g. osteomyelitis and prostatitis, etc), where the causative organism is known to be sensitive to ciprofloxacin, should be treated for at least three days after the signs and symptoms of the infection have disappeared.

For acute pulmonary exacerbations 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 in patients who have shown hypersensitivity to ciprofloxacin or other quinolone anti-infectives.
Except in cases of exacerbations of cystic fibrosis associated with *P. aeruginosa* (in patients aged 5-17 years), ciprofloxacin is contra-indicated in children and growing adolescents unless the benefits of treatment are considered to outweigh the risks.

4.4 Special warnings and precautions for use

Prolonged, disabling and potentially irreversible serious adverse drug reactions:

Cases of prolonged (continuing for months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (including musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. Ciprofloxacin 250 mg, film coated tablets should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber

for advice, so that symptoms can be appropriately investigated and to avoid further exposure which could potentially worsen adverse reactions.

Ciprofloxacin should be used with caution in epileptics and patients with a history of CNS 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).

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.

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 the first sign of pain or inflammation, patients should discontinue ciprofloxacin and rest the affected limbs.

There is a risk of pseudomembranous colitis with broad-spectrum antibiotics. 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).

As with other quinolones, patients should avoid prolonged exposure to strong sunlight or UV radiation during treatment.

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.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interactions with Other Medicaments 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. Where 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.

Phenytoin levels may be altered when Ciprofloxacin is used concomitantly.

Ciprofloxacin film coated tablets should not be administered within 4 hours of medications containing magnesium, aluminium, calcium or iron salts 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.

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

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.

The simultaneous administration of quinolones and glibenclamide can on occasion potentiate the effect of glibenclamide resulting in hypoglycaemia.

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.

When ciprofloxacin is used for surgical prophylaxis, it is recommended that opiate premedicants, (e.g. papaveretum) or opiate premedicants used with anticholinergic premedicants, (e.g. atropine or hyoscine) are not used, as the serum levels of ciprofloxacin are reduced and adequate cover may not be obtained during surgery. Co-administration of ciprofloxacin and benzodiazepine premedicants has been shown not to affect ciprofloxacin plasma levels.

4.6 Pregnancy and Lactation

Pregnancy

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.

Lactation

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

Cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, fatigue, psychiatric symptoms, memory impairment, and impairment of hearing, vision, taste and smell) have been reported in association with the use of quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see section 4.4). A range of psychiatric symptoms may occur as part of these side effects, which may include, but are not necessarily limited to, sleep disorders, anxiety, panic attacks, confusion, or depression. There are no pharmacological treatments established to be effective treatments of the symptoms of long lasting or disabling side effects associated with fluoroquinolones. The frequency of these prolonged, disabling and potentially irreversible serious drug reactions cannot be estimated with precision using available data, but the reporting incidence from adverse drug reaction reports indicates the frequency is at minimum between 1/1,000 and 1/10,000 (corresponding to the Rare frequency category).

Ciprofloxacin is generally well tolerated. The most frequently reported adverse reactions are nausea, diarrhoea and rash.

Blood and the lymphatic system disorders

Anaemia, eosinophilia, increases or decreases in white cell and/or platelet count, altered prothrombin levels.

Very rarely: haemolytic anaemia, agranulocytosis or pancytopenia.

Metabolism and nutrition disorders
Hyperglycaemia.

Nervous system disorders
Headache, restlessness, depression, dizziness, tremor, convulsions, confusion, hallucinations, somnolence, sleep disorders.

Very rarely: migraine and anxiety states.

Isolated cases of ciprofloxacin-induced psychoses have been reported, which may progress to self-endangering behaviour.

Paresthesia has been

reported. Eye disorders

Very rarely: visual disturbances including diplopia and colour disturbances.

Ear and labyrinth disorders
Very rarely: tinnitus, transient impairment of hearing particularly at high frequencies.

Cardiac
disorders
Tachycardia

Vascular disorders
Oedema, fainting, hot flushes and sweating.
Very rarely: vasculitis.
There are isolated reports of intracranial hypertension associated with quinolone therapy.

Gastrointestinal disorders
Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, anorexia, flatulence, dusphagia.
Rarely: pseudomembranous colitis.

Hepato-biliary disorders
Transient increases in liver enzymes or serum bilirubin (particularly in patients with previous liver damage), hepatitis, jaundice/cholestasis and major liver disorders including hepatic necrosis, which may rarely progress to hepatic failure.
Abnormal laboratory findings, e.g. increased alkaline phosphatase, increases in liver function tests, e.g. transaminases, and cholestatic jaundice, especially in patients with previous liver damage.

Hypersensitivity and skin reactions
Drug-induced fever, anaphylactoid reactions including angioedema and dyspnoea, and serum sickness-like reaction.

Rash, pruritis, urticaria, photosensitivity.

Rarely: erythema nodosum and erythema multiforme.

Very rarely: petechiae, haemorrhagic bullae, Stevens-Johnson syndrome – Lyells Syndrome.

Treatment with ciprofloxacin should be discontinued if any of the above occur upon first administration.

Musculoskeletal, connective tissue and bone disorders
Reversible arthralgia, joint swelling and myalgia.
Rarely: tenosynovitis, exacerbation of the symptoms of myasthenia gravis.

Tendon inflammation (predominantly of the Achilles tendon) has been reported which may lead to tendon rupture (Rare (≥1/10,000 to <1/1,000)).

Treatment should be discontinued immediately if these symptoms occur.

Renal and urinary disorders
Transient increases in blood urea or serum creatinine, renal failure, crystalluria, haematuria, nephritis.

General disorders and administration site conditions
Moniliasis, asthenia, abnormal gait.

Very rarely: impaired taste and smell usually reversible upon discontinuation of treatment.

4.9 Overdose

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. Calcium or magnesium antacids may be administered as soon as possible after ingestion of Ciprofloxacin film coated tablets in order to reduce the absorption of ciprofloxacin.

Serum levels of ciprofloxacin are reduced by dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

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.

Breakpoints
$S \leq 1$ µg/ml, $R \geq 4$ µg/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.

Organism	Prevalence of Resistance
Sensitive:	
Gram-positive bacteria	
Corynebacterium diphtheriae	0%
Corynebacterium spp.	-
Staphylococcus aureus (methicillin sensitive)	0 - 14%
Staphylococcus aureus (methicillin resistant)	48 - 90%
Streptococcus agalactiae	0 - 17%
Gram-negative bacteria	
Acinetobacter baumanii	6 - 93%
Acinetobacter spp.	14 - 70%
Aeromonas hydrophilia	0%
Aeromonas spp.	-
Bordetella pertussis	0%
Brucella melitensis	0%
Campylobacter jejuni/coli	0 - 82%
Campylobacter spp.	0%
Citrobacter freundii	0 - 4%
Citrobacter spp.	0%
Edwardsiella tarda	0%
Enterobacter aerogenes	0%
Enterobacter cloacae	0 - 3%
Enterobacter spp.	3 - 13%
Escherichia coli	2 -7%
Escherichia coli, EHEC and EPEC	-
Haemophilus influenzae	0 - 1%
Haemophilus influenzae (ß-lactam negative)	0%
Haemophilus influenzae (ß-lactam positive)	0%
Haemophilus parainfluenzae	0%
Hafnia alvei	0%
Klebsiella oxytoca	0%
Klebsiella pneumoniae	2 - 5.8%
Klebsiella spp.	2 - 21%
Legionella pneumophila	0%
Legionella spp.	0%
Moraxella catarrhalis	0%
Morganella morganii	1 - 2%
Neisseria gonorrhoeae	0%

Neisseria gonorrhoeae, ß-lactamase	0%
Neisseria gonorrhoeae, ß-lactamase positive	0%
Neisseria meningitidis	0%
Neisseria meningitidis, ß-lactamase negative	0%
Plesiomonas shigelloides	0%
Proteus mirabilis	0 - 10%
Proteus vulgaris	4%
Providencia rettgeri	-
Providencia spp.	4%
Providencia stuartii	-
Pseudomonas aeruginosa	1 - 28%
Salmonella spp.	0%
Salmonella typhi	0 - 2%
Serratia liquefaciens	-
Serratia marcescens	23%
Serratia spp.	0 - 21%
Shigella spp.	0%
Vibrio cholerae	0%
Vibrio parahaemolyticus	0%
Vibrio spp.	0%
Yersinia enterocolitica	0%
Anaerobes	
Bacteroides ureolyticus	0%
Clostridium perfringens	-
Peptococcus spp.	0%
Peptostreptococcus spp.	-
Peptostreptococcus magnus	0%
Veillonella parvula	0%
Other pathogens	
Chlamydia spp.	-
Helicobacter pylori	-
Mycobacterium fortuitum	0%
Mycobacterium tuberculosis	0%
Mycoplasma hominis	16%

Intermediate	
Gram-positive aerobes	
Enterococci	5%
Enterococcus faecalis	9 - 34%
Staphylococcus epidermis, methicillin sensitive	10 - 16%

Staphylococcus epidermis, methicillin resistant	26 - 56%	
Staphylococcus haemolyticus	-	
Staphylococcus haemolyticus, methicillin sensitive	8%	
Staphylococcus haemolyticus, methicillin resistant	73%	
Streptococcus anginosus	9%	
Streptococcus bovis	-	
Streptococcus milleri		5%
Streptococcus mitis		-
Streptococcus pneumoniae, penicillin sensitive		0 - 1%
Streptococcus pneumoniae, penicillin intermediate		-
Streptococcus pneumoniae, penicillin intermediate and resistant		2.8%
Streptococcus pneumoniae, penicillin resistant		-
Streptococcus pyogenes		0 - 28%
Streptococcus, viridans group		-
Streptococcus viridans, penicillin sensitive		-
Streptococcus viridans, penicillin resistant		-
Streptococcus, ß-haemolytic groups A, C, and G		0%
Gram-negative aerobes		
Alcaligenes spp.		-
Listeria monocytogenes		0%
Listeria spp.		0%
Anaerobes		
Fusobacterium spp.		-
Gardnerella vaginalis		0%
Prevotella spp.		-
Other pathogens		
Ureaplasma urealyticum	11%	
Resistant		
Gram-positive aerobes		
Enterococcus faecium	-	
Stenotrophomonas maltophilia	94%	
Streptococcus sanguis	-	
Gram-negative aerobes		
Flavobacterium meningosepticum	-	
Nocardia asteroides	-	
Anaerobes		
Bacteroides fragilis	-	

Bacteroides thetaiotaomicron	-
Clostridium difficile	-

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 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 0.5-2.0 hours after dosing. The AUC also increases dose proportionately after administration of both single and repeated oral (tablet) and intravenous doses. 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 a 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 times daily are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimen.

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 crystalluria, 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 rats and dogs treated with ciprofloxacin was noted in repeat dose toxicity testing. This was more noticeable in the dog. Although analysis of available safety data from ciprofloxacin use in paediatric patients did not disclose any evidence of drug related cartilage or articular damage, the use of ciprofloxacin in children and growing adolescents is generally not recommended, unless the benefits are considered to outweigh the potential risks (with the exception of treatment of cystic fibrosis). Additionally, because of the potential of arthropathy, the use of ciprofloxacin during pregnancy and lactation is not recommended.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lactose monohydrate
Sodium starch glycollate
Povidone
Sodium stearyl fumarate
Opadry Y-1-7000 White (hypromellose, macrogol and titanium dioxide)

6.2. Incompatibilities

Not applicable.

6.3. Shelf Life

3 years.

6.4. Special Precautions for Storage

Do not store above 25°C.

6.5. Nature and Contents of Container

Blister strips in cardboard outers comprising:

PVC/Aluminium blister strips
Pack size: 10 and 20 tablets

6.6. Instruction for Use/Handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

PL 18374/0004

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