IRISH MEDICINES BOARD ACT 1995

MEDICINAL PRODUCTS(LICENSING AND SALE)REGULATIONS, 1998

(S.I. No.142 of 1998)

PPA1328/074/001
Case No: 2029783

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

B & S Healthcare

Unit 4, Bradfield Road, **Ruislip**, **Middlesex**, **HA4 0NU**, **United Kingdom**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Ciproxin 250 mg Film-Coated Tablets

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **13/04/2007** until **12/04/2012**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ciproxin 250 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains 291.0mg ciprofloxacin hydrochloride equivalent to 250mg Ciprofloxacin.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Product imported from Italy:
Film-coated tablet, round, white to slightly yellow, marked with Bayer cross on one side and 'CIP', a breakline and '250' impressed on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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 (see Section 4.4). In circumstances where a physician considers it appropriate to use ciprofloxacin in patients with pneumococcal pneumonia, a dose of 750mg twice daily should provide adequate cover in the majority of cases (see Section 4.2). Ciprofloxacin may be used for treating Gram-negative pneumonia.
Urinary tract infections: e.g. uncomplicated and complicated urethritis, cystitis, pyelonephritis, prostatitis, epididymitis.
Gastro-intestinal infections: e.g. enteric fever, infective diarrhoea.
Gonorrhoea: including urethral, rectal and pharyngeal gonorrhoea caused by beta-lactamase producing organisms or organisms moderately sensitive to penicillin.

Children:

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

Inhalation Anthrax in Adults and Children: To reduce the incidence or progression of disease following confirmed or suspected exposure to aerosolised *Bacillus anthracis.*

4.2 Posology and method of administration

General dosage recommendations: the dosage of ciprofloxacin 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. Ciproxin Tablets should be swallowed whole with an adequate amount of liquid.
If Ciproxin 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 fortified orange juice). However, a normal diet that will contain small amounts of calcium, does not significantly affect ciprofloxacin absorption.

Adults

The dosage range for adults is 100-750mg 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
Acute, uncomplicated cystitis	100mg b.d. or 250mg b.d.**
Upper and lower urinary tract infections (depending on severity)	250-500mg b.d.
Upper and lower respiratory tract infections (depending on severity)	250-750mg b.d.
Pneumococcal pneumonia (second-line where physician considers it appropriate)	750mg b.d.
Cystic fibrosis patients with pseudomonal lower RTI *	750mg b.d.
Other infections	500-750mg b.d.
Severe infections, particularly due to Pseudomonas, staphylococci and streptococci	750mg b.d.
Inhalation Anthrax	500mg b.d.

* As the pharmacokinetics of ciprofloxacin remain unchanged in patients with cystic fibrosis, the low bodyweight of these patients should be taken into consideration when determining dosage.
** Both doses are equally effective in treating acute, uncomplicated cystitis.

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. Dialysis reduces serum levels of ciprofloxacin.

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 exacerbation associated with *P. aeruginosa* infection, at a dose of 20mg/kg orally twice daily (maximum daily dose 1500mg).
For the indication of inhalation anthrax, the risk-benefit assessment indicates that administration of ciprofloxacin to paediatric patients at a dose of 15 mg/kg orally twice daily (maximum daily dose of 1000 mg) is appropriate.
For indications other than treatment of pulmonary exacerbations in cystic fibrosis and inhalation anthrax, 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 Ciproxin 100mg Tablets or Ciproxin 250mg Tablets.
In other acute infections the usual treatment period is 5 to 10 days with Ciproxin 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.
For inhalation anthrax, drug administration should begin as soon as possible after confirmed or suspected exposure and should be continued for 60 days.

4.3 Contraindications

Ciprofloxacin is contra-indicated in patients who have shown hypersensitivity to ciprofloxacin or any of the excipients, or other quinolone anti-infectives, or who have a history of quinolone-induced tendon disorder.
Ciprofloxacin is also contra-indicated in children and growing adolescents unless epiphyseal closures of long bones have occurred or except where the benefits of treatment exceed the risks.
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).
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 the first sign 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, 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.
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 4mg was given. There was an increase in tizanidine serum concentrations (Cmax 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).

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 Cmax 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 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 cyclosporin. 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 can on occasion potentiate the effect of glibenclamide resulting in hypoglycaemia.

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This may increase the risk of methotrexate associated 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 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 child-bearing 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

The most frequently reported adverse reactions are nausea, diarrhoea and rash.
The following adverse reactions have been observed:

Effects on the gastrointestinal system

Common (> 1/100, <1/10): nausea, diarrhoea

Uncommon (> 1/1,000, < 1/100): SGOT increased, SGPT increased, vomiting, dyspepsia, abnormal liver function test, alkaline phosphatase increased, anorexia, flatulence, bilirubinaemia.
Rare (> 1/10,000, < 1/1,000): moniliasis (oral), jaundice, cholestatic jaundice, pseudomembranous colitis, dysphagia
Very rare (< 1/10,000): moniliasis (gastrointestinal), hepatitis, liver necrosis (very rarely progressing to life threatening hepatic failure), life threatening pseudomembranous colitis with possible fatal outcome, pancreatitis

Effects on the body as a whole

Uncommon (> 1/1,000, < 1/100): abdominal pain, moniliasis, asthenia (general feeling of weakness, tiredness).
Rare (> 1/10,000, < 1/1,000): pain, pain in extremeties, back pain, chest pain

Effects on the cardiovascular system

Rare (> 1/10,000, < 1/1,000): tachycardia, migraine, syncope (fainting), vasodilation (hot flushes), hypotension
Very rare (< 1/10,000): vaculitis (petechiae, haemorrhagic bullae, papules, crust formation)

Effects on the hemic and lymphatic system

Uncommon (> 1/1,000, < 1/100): eosinophilia, leukopenia
Rare (> 1/10,000, < 1/1,000): anaemia, leukopenia (granulocytopenia), leucocytosis, altered prothrombin values, thrombocytopenia, thrombocythaemia (thrombocytosis)
Very rare (< 1/10,000): hemolytic anaemia, petechia (punctate skin haemorrhages), agranulocytosis, pancytopenia (life threatening), bone marrow depression (life threatening)

Metabolic and nutritional disorders

Uncommon (> 1/1,000, < 1/100): increases in creatinine, increases in BUN (urea)
Rare (> 1/10,000, < 1/1,000): oedema (peripheral, vascular, face), hyperglycaemia
Very rare (< 1/10,000): amylase increased, lipase increased

Effects on the musculoskeletal system

Uncommon (> 1/1,000, < 1/100): arthralgia (joint pain)
Rare (> 1/10,000, < 1/1,000): myalgia (muscular pain), joint disorder (joint swelling)
Very rare (< 1/10,000): myasthenia, tendinitis (predominantly achillo tendinitis including tenosynovitis), partial or complete tendon rupture (predominantly achilles tendon), exacerbation of symptoms of myasthenia gravis. Treatment should be discontinued immediately if tendinitis or complete tendon rupture occur.

Effects on the nervous system

Uncommon (> 1/1,000, < 1/100): headache, dizziness, insomnia, agitation, confusion
Rare (> 1/10,000, < 1/1,000): hallucination, sweating, paresthesia (peripheral paralgesia), anxiety, abnormal dreams (nightmares), depression, tremor (trembling), convulsion, hypesthesia, somnolence
Very rare (< 1/10,000): grand mal convulsion, abnormal (unsteady) gait, psychosis (which may progress to self-endangering behaviour), intracranial hypertension, ataxia, hyperesthesia, hypertonia, twitching

Effects on the respiratory system

Rare (> 1/10,000, < 1/1,000): dyspnoea, larynx oedema

Effects on the skin and appendages

Common (> 1/100, <1/10): rash
Uncommon (> 1/1,000, < 1/100): pruritis, maculopapular rash, urticaria
Rare (> 1/10,000, < 1/1,000): photosensitivity reaction

Very rare (< 1/10,000): petechia, erythema mutliforme (minor), erythema nodosum, Stevens-Johnson-Syndrome, epidermal necrolysis (Lyell-Syndrome), fixed drug reaction

Effects on special senses

Uncommon (> 1/1,000, < 1/100): taste perversion (usually reversible upon discontinuation of treatment).
Rare (> 1/10,000, < 1/1,000): tinnitus, transitory deafness (especially at high frequencies), abnormal vision (visual disturbances), diplopia, chromatopsia, taste loss (impaired taste)
Very rare (< 1/10,000): parosmia (impaired smell), anosmia (usually reversible on discontinuation)

Hypersensitivity reactions

Rare (> 1/10,000, < 1/1,000): allergic reaction, drug fever, anaphylactoid (anaphylactic) reaction.
Very rare (< 1/10,000): shock (anaphylactic/anaphylactoid reactions progressing in very rare cases to life threatening shock), pruritic rash, serum sickness like reaction, angioedema

Effects on the urogenital system

Rare (> 1/10,000, < 1/1,000): acute kidney failure, abnormal kidney function, vaginal moniliasis, haematuria, crystalluria, interstitial nephritis

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 Ciproxin Tablets in order to reduce the absorption of ciprofloxacin.
Serum levels of ciprofloxacin are reduced by dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code J01 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.

Breakpoints

S ≤ 1 μg/ml, R ≥ 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%
Bacillus anthracis	-
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 (β (-lactam negative)	0%
Haemophilus influenzae (β -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, β-lactamase	0%
Neisseria gonorrhoeae, β-lactamase positive	0%
Neisseria meningitidis	0%
Neisseria meningitidis, β-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, β-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	-

Resistance

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. Plasma levels peak approximately 1.5-2.5 hours after dosing and the $AUC_{0-\alpha}$ 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 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.
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 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 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

Each tablet core contains:
microcrystalline cellulose,
maize starch,
crospovidone,
colloidal anhydrous silica,
magnesium stearate.

The tablet film-coat consists of a mixture of:
hypromellose
Macrogol,
Titanium dioxide (E171).

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

The shelf-life expiry date of this product shall be the date shown on the container and outer package of the product on the market in the country of origin.

6.4 Special precautions for storage

No special storage precautions are necessary.

6.5 Nature and contents of container

Blister strips in cardboard outers
Pack size 10 tablets.

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 Parallel Product Authorisation Holder

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8 Parallel Product Authorisation Number

PPA 1328/74/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation 13th April 2007.

10 DATE OF REVISION OF THE TEXT