IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1044/002/003
Case No: 2051936

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

Kellpharm Limited

20A Beckett Way, **Parkwest**, **Dublin 12**

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

Profloxin 750 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 **21/07/2008** until **27/01/2010**.

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

Profloxin 750 mg film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One film-coated tablet contains ciprofloxacin hydrochloride equivalent to 750mg ciprofloxacin.

For excipients see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

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

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

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 Special Warnings and Precautions for use).

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 Posology and method of administration). 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.

Gonorrhea: including urethral, rectal and pharyngeal gonorrhea caused by beta-lactamase producing organisms or organisms moderately sensitive to penicillin.

4.2 Posology and method of administration

General dosage recommendations: the dosage of ciprofloxacin 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 tablets should be swallowed whole with an adequate amount of liquid.

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	250 mg single dose
Acute, uncomplicated cystitis	250 mg b.d.
Upper and lower urinary tract infections (depending on severity)	250 - 500 mg b.d.
Upper and lower respiratory tract infections (depending on severity)	250 - 750 mg b.d.
Pneumococcal pneumonia (second line where physician considers it appropriate)	750 mg b.d.
Cystic fibrosis patients with pseudomonal lower RTI*	750 mg b.d.
Other Infections	500-750 mg b.d.
Severe infections, particularly due to Pseudomonas, Staphylococci and Streptococci	750 mg 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.

Impaired renal function Dosage adjustments are not usually required, except in patients with severe renal impairment (serum creatinine >265 micromole/l or creatinine clearance <20 ml/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 the relevance of this to man is unknown, its use in children and growing adolescents is not recommended. However, where the benefit of using ciprofloxacin is considered to outweigh this potential risk, the dosage should depend upon the severity of infection and be administered in two divided doses.

Duration of treatment The duration of treatment depends upon the severity of infection, clinical response and bacteriological findings.
In acute infections the usual treatment period is 5 to 10 days with ciprofloxacin tablets. In acute uncomplicated cystitis the treatment period is three days.
Generally, treatment should be continued for at least 3 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. Initial intravenous administration may be followed by treatment with oral ciprofloxacin.

4.3 Contraindications

Ciprofloxacin is contra-indicated in patients who have shown hypersensitivity to ciprofloxacin or similar quinolones.
Ciprofloxacin is contra-indicated in patients with 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 where the benefits of treatment exceed the risks.

4.4 Special warnings and precautions for use

Ciprofloxacin should only be administered with great caution to patients with existing central nervous system disorders, including epilepsy, or history of convulsive disease.

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.

Persons with latent or actual defects in glucose-6-phosphate dehydrogenase activity are prone to haemolytic reactions with quinolone antibacterials, 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 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 the 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Ciprofloxacin 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.

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.

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.

Prolongation of bleeding time has been reported during concomitant administration of ciprofloxacin and anticoagulants.

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 hypoglycemia.

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

In animal studies ciprofloxacin causes disordered collagen and bone deposition in areas of bone growth, as do other drugs of this series. The drug produced these effects in animals in reproduction studies. It crosses the placenta and is excreted in breast milk and amniotic fluid.

It should not be used during pregnancy, or in women at risk of pregnancy, nor during lactation.

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

Gastro-intestinal disturbances: including rarely, pseudomembranous colitis.

CNS disturbances, e.g. headache, restlessness, depression, dizziness, tremor, convulsions, confusion, hallucinations, somnolence. Very rarely, sleep disorders and anxiety states. Isolated cases of ciprofloxacin-induced psychoses have been reported.
There are isolated reports of intracranial hypertension associated with quinolone therapy.

Hypersensitivity/skin, e.g. rash, pruritus, urticaria, photosensitivity, drug-induced fever, anaphylactic/ anaphylactoid reactions. Rarely erythema nodosum and erythema multiforme. Very rarely, petechiae, haemorrhagic bullae, vasculitis, Stevens-Johnson syndrome and Lyell’s Syndrome. Treatment with ciprofloxacin should be discontinued if any of the above occurs upon first administration.

Hepatic disturbances, e.g. transient increases in liver enzymes or serum bilirubin (particularly in patients with previous liver damage), hepatitis, jaundice and major liver disorders including hepatic necrosis, which may rarely progress to hepatic failure.

Renal disturbances.

Musculoskeletal disturbances, e.g. reversible arthralgia, joint swelling and myalgia. Rarely tenosynovitis and very rarely tendon inflammation, which may lead to tendon rupture.

Effects on haematological parameters, e.g. eosinophilia, leucopenia, granulocytopenia, thrombocytopenia, thrombocytosis, altered prothrombin levels and very rarely haemolytic anaemia.

Special sense disturbances, e.g. very rarely, visual disturbances, impaired taste and smell, tinnitus, transient impairment of hearing particularly at high frequencies.

Tachycardia has been reported.

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 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 bacterial effect against sensitive organisms and it is often found that minimum bacterial concentrations are in the range of minimum inhibitory concentrations. Ciprofloxacin has been shown to have no activity against *Treponema pallidum* and *Ureaplasma urealyticum*, *Nocardia asteroids*, and *Enterococcus faecium* are resistant.

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 $AUC_{0-\infty}$ is in the range of 5-12 mg.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 <20 ml/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 creatinine clearance. However, it is recommended that in severely renally impaired patients, the total daily dosage should be reduced by half, although monitoring of drug serum levels provides the most reliable basis for dose adjustment as necessary.

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 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, 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
Colloidal anhydrous silica
Magnesium stearate
Hypromellose
Macrogol 400
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

5 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Blister strips consisting of 250 µm clear PVC and 20 µm hard temper aluminium foil contained in a carton.
Pack sizes: 5, 10, 12, 20, 30, 50, 60, 90 film-coated 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 requirement.

7 MARKETING AUTHORISATION HOLDER

Kellpharm Limited
20A Beckett Way
Parkwest
Dublin 12

8 MARKETING AUTHORISATION NUMBER

PA 1044/2/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 28th January 2005

10 DATE OF REVISION OF THE TEXT

June 2007