Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Truoxin 250 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ciprofloxacin 250 mg as the hydrochloride.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White or yellowish, scored, 11 mm round, biconvex, film-coated tablets. Scored on both sides and side wall scored, marked C250 on one side.

The tablets 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 (see section 4.4 and 5.1Particular attention should be paid to available information on resistance to ciprofloxacin before starting treatment.

Adults
Upper and lowerres piratory tract infections:
- Exacerbation of chronic obstructive pulmonary disease. In acute exacerbations of chronic obstructive pulmonary disease including chronic bronchitis, Truoxin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for treatment of these infections.
- Gram-negative pneumonia (but not first-line therapy for pneumococcal pneumonia).
- Broncho-pulmonary infections in cystic fibrosis or in bronchiectasis
- Chronic suppurative otitis media
- Acute exacerbation of chronic sinusitis especially if these are caused by Gram-negative bacteria

Urinary tract infections:
- Uncomplicated acute cystitis: In uncomplicated acute cystitis, Truoxin should be used only when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the treatment of these infections.
- Acute pyelonephritis
- Complicated urinary tract infections
- Bacterial prostatitis

Genital tract infections:
- gonococcal uretritis and cervicitis due to susceptible *Neisseria gonorrhoeae*
- *epididymo-orchitis including cases due to susceptible Neisseriagonorrhoeae*
- *pelvic inflammatory disease including cases due to susceptible Neisseriagonorrhoeae*

-*Gastro-intestinal infections:* e.g. enteric fever, infective diarrhoea, travellers' diarrhoea
-*Intra-abdominalinfections*
-*In*fections of the skin and soft tissue caused by Gram-negative bacteria
-Malignant external otitis
-Infections of the bones and joints
-Prophylaxis of invasive infections due to *Neisseriameningitides*
-Inhalation anthrax (post-exposure prophylaxis and curative treatment

Ciprofloxacin may be used in the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.

Children and adolescents
- Bronchopulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis
- Complicated urinary tract infections and acute pyelonephritis
- Inhalation anthrax (post-exposure prophylaxis and curative treatment)

Ciprofloxacin may also be used to treat severe infections in children and adolescents when this is considered to be necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

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

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. Treatment of infections due to certain bacteria (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* or *Staphylococci)* may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.

Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.

Adults:
Lower respiratory tract infections:
500mg 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.

Upper respiratory tract infections (see section 4.4):
Acute exacerbation of chronic sinusitis: 500mg to 750mg twice daily for 7 to 14 days *Chronic suppurative otitis media:* 500mg to 750mg twice daily for 7 to 14 days *Malignant external otitis:* 750mg twice daily for 28 days up to 3 months.

*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: 250mg to 500mg twice a day for 3 days. In pre-menopausal women, 500mg single dose may be used.
Complicated cystitis, acute pyelonephritis: 500mg twice daily for 7 days.
Bacterial prostatitis: 500mg to 750mg twice daily, 2 to 4 weeks (acute) to 4 to 6 weeks (chronic).
Complicated infections and pyelonephritis: 500mg to 750mg twice daily. Usual duration of treatment 7 –14 days, it can be continued for longer than 21 days in some specific circumstances (such as abscesses).

Genital tract infections:
Gonococcal uretritis and cervicitis: 500 mg as a single dose
Epididymo-orchitis and pelvic inflammatory diseases: 500mg to 750mg twice daily for at least 14 days

Gastrointestinal infections and intra-abdominal infections:
- Diarrhoea caused by bacterial pathogens including *Shigella* spp. other than S*higella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea: 500mg twice daily, for 1 day
- Diarrhoea caused by *Shigella dystenteriae* type 1: 500mg twice daily for 5 days
- Diarrhoea caused by *Vibrio cholera*: 500mg twice daily for 3 days
- Typhoid fever: 500mg twice daily for 7 days

- Intra-abdominal infections due to Gram-negative bacteria: 500mg to 750mg twice daily for 5 to 14 days

Infections of the skin and soft tissue:
500mg to 750mg twice daily for 7 to 14 days

Bone and joint infections:
500mg to 750mg twice daily for a maximum of 3 months

Neutropenic patients with fever that is suspected to be due to a bacterial infection: Ciprofloxacin should be co- administered with appropriate antibacterial agent(s) in accordance to official guidance.
500mg to 750mg twice daily which should be continued over the entire period of neutropenia

Prophylaxis of invasive infections due to Neisseria meningitidis:
500mg as a single dose

For *inhalation anthrax post-exposure prophylaxis*and curative treatment for persons able to receive treatment by oral route when clinically appropriate, drug administration should begin as soon as possible after suspected or confirmed exposure. 500mg should be administered twice daily for 60 days from the confirmation of *Bacillus anthracis* exposure.

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 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 is the paediatric population is generally not recommended.

Cystic fibrosis:
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 10 to 14 days.

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.

Complicated urinary tract infections and acute pyelonephritis:
10 mg/kg body weight twice daily to 20 mg/kg body weight twice daily with a maximum of 750 mg per dose for 10 to 21 days

*For inhalation anthrax post exposure prophylaxis*and curative treatment for persons able to receive treatment by oral route when clinically appropriate, drug administration should begin as soon as possible after suspected or confirmed exposure.
10 mg/kg body weight twice daily to 15 mg/kg body weight twice daily with a maximum of 500 mg per dose for 60 days from the confirmation of *Bacillus anthracis* exposure.

Other severe infections:
20 mg/kg body weight twice daily with a maximum of 750 mg per dose according to the type of infections

Elderly:
Although higher ciprofloxacin serum levels are found in the elderly, no adjustment of dosage is necessary. Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.

Patients with renal and hepatic impairment:

Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine Clearance [Ml/min/1.73 m^2]	**Serum Creatinine [µmol/L]**	**Oral Dose [mg]**
> 60	< 124	See Usual Dosage.
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)

Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.

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

Method of administration
Tablets should be swallowed whole with fluid. If 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.

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.

In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

4.3 Contraindications

- Hypersensitivity to ciprofloxacin, other quinolone antibiotics, or any of the excipients listed in section 6.1.
- 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 (see section 4.5).

4.4 Special warnings and precautions for use

The use of Truoxin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products (see section 4.8). Treatment of these patients with Truoxin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3)

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. Truoxin 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.

Tendonitis and tendon rupture
Tendonitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendonitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.

At first sign of tendonitis (e.g. painful swelling, inflammation) the treatment with Truoxin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.

Streptococcal infections (including *Streptococcus pneumoniae*)
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy. 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.

Vision disorders
If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately (see section 4.8).

Genital tract infections
Gonococcal uretritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolones-resistant *Neisseria gonorrhoeae* isolates.

Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e.g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Urinary tract infections
Resistance to fluoroquinolones of *Escherichia coli* – the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in *Escherichia coli* to fluoroquinolones.

The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of *Escherichia coli* to quinolones.

Intra-abdominal infections
There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea
The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints
Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax
Use in humans is based on *in-vitro* susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

Paediatric population
The use of ciprofloxacin in children and adolescents should follow available official guidance. Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.

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.

Ciprofloxacin has been shown to cause arthropathy in weight bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue. (See section 4.8)

Bronchopulmonary infections in cystic fibrosis
Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.

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.

Complicated urinary tract infections and pyelonephritis
Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.

Clinical trials have included children and adolescents aged 1-17 years.

Other specific severe infections
Ciprofloxacin may be considered for other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify ciprofloxacin use.

The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.

Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur after the first administration (see section 4.8) and may be life threatening. If such reaction occurs, therapy should be discontinued and an adequate medical treatment is required.

Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendonitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur with quinolone antibiotics, even within the first 48 hours of treatment. Inflammation and rupture of tendons may occur up to several months after discontinuation of ciprofloxacin therapy. Such reactions have been observed particularly in older patients or in patients treated concurrently with corticosteroids (see section 4.8). At first signs of pain or inflammation, patients should discontinue ciprofloxacin and rest the affected limbs.

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated (see section 4.8).

Photosensitivity
Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light during treatment (see section 4.8). Therapy should be discontinued if photosensitisation (i.e., sunburn-like skin reaction) occurs.

Central Nervous System
Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued (see section 4.8). Psychiatric reactions have been reported after first administration of ciprofloxacin in some patients. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. Treatment should be discontinued if side-effects, depression or psychoses lead to self-endangering behaviour.

Cases of polyneuropathy (based on neurological symptoms such as pain, burning, sensory disturbances or muscle weakness, alone or in combination) have been reported in patients receiving ciprofloxacin.

Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy including; pain, burning, tingling, numbness, and/or weakness in order to prevent the development of an irreversible condition (see section 4.8).

Cardiac disorders
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example, congenital long QT syndrome, concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics), uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia), cardiac disease (e.g. heart failure, myocardial infarction, bradycardia).

Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9).

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported (see section 4.8), usually in diabetic patients, receiving concomitant treatment with an oral hypoglycaemic agent (e.g. glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.

Gastrointestinal System
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.

Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function
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. Dose adjustment is needed in patients with impaired renal function as described in section 4.2 to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin (see section 4.8). In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued.

Glucose-6-phophate dehydrogenase deficiency
Patients with glucose-6-phophate dehydrogenase deficiency (or a family history of) are prone to haemolytic reactions with quinolones, and so ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the risks. In this case, potential occurrence of haemolysis should be monitored.

Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by *Staphylococcus* and *Pseudomonas* species.

Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin and tizanidine is contra-indicated.

Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary (see section 4.5).

Methotrexate
The concomitant use of ciprofloxacin with methotrexate is not recommended (see section 4.5)

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.

The *in-vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.

Risk of aortic aneurysm and dissection
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.

Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Peripheral neuropathy
Cases of sensorimotor polyneuropathy resulting in paraesthia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Truoxin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition. (see section 4.8)

4.5 Interaction with other medicinal products and other forms of interactions

Effects of other products on ciprofloxacin

Drugs known to prolong QT interval
Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see section 4.4).

Chelation Complex Formation
The simultaneous administration of ciprofloxacin (oral) and multivalent cation containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin.

Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H2 receptor blockers.

Food and Dairy Products
The concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with 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.

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

Metoclopramide

The use of metoclopramide with ciprofloxacin may accelerate the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole
Concomitant administration of ciprofloxacin and Omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of ciprofloxacin.

Effects of ciprofloxacin on other medicinal products:

Tizanidine
Tizanidine must not be administered together with ciprofloxacin (see section 4.3).

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 (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. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate
Renal tubular transport 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. The concomitant use is not recommended (see section 4.4).

Theophylline
Increased plasma levels of theophylline have been observed following concurrent administration with ciprofloxacin. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. It is recommended that the dose of theophylline be reduced as necessary (see section 4.4) and plasma levels of theophylline be monitored. 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.

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.

Phenytoin
Phenytoin serum levels may be altered when ciprofloxacin is used concomitantly. Monitoring of drug levels is recommended.

Cyclosporin
Transient increases in the concentration of serum creatinine have been seen following concomitant administration of ciprofloxacin and cyclosporin. Therefore, monitoring of serum creatinine levels (twice a week) is advisable.

Vitamin K antagonists
Simultaneous administration of ciprofloxacin with a vitamin K antagonist may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Duloxetine
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 (see section 4.4).

Ropinirole
It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of Cmax and AUC of ropinirole by 60% and 84%, respectively.

Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin (see section 4.4).

Lidocaine

It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. Although lidocaine treatment was well tolerated, a possible interaction with ciprofloxacin associated with side effects may occur upon concomitant administration.

Clozapine
Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with ciprofloxacin are advised (see section 4.4).

Sildenafil
Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.

Tacrine
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. tacrine) Therefore, patients taking tacrine concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations.

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

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

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)
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. Concomitant use with some phenylpropionic acid-derived non-steroidal anti-inflammatory drugs may lead to toxicity possibly because of renal effects.

Agomelatine
In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see 'Cytochrome P450' in section 4.4).

Zolpidem
Co-administration of ciprofloxacin may increase blood levels of zolpidem, concurrent use is not recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or feto/neonatal toxicity of ciprofloxacin.

Reproduction studies performed in mice, rats and rabbits using parenteral and oral administration did not reveal any direct or indirect harmful effects of reproductive toxicity (teratogenicity, impairment of fertility or impairment of peri-/post-natal development). In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus (see section 5.3). Therefore, as a precautionary measure, its use during pregnancy is not recommended.

Breast-feeding
Studies have indicated that ciprofloxacin is secreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.

4.7 Effects on ability to drive and use machines

Due to its neurological effect, 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 commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea. ADRs derived from clinical studies and post-marketing surveillance with ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.

System Organ Class	**Common ≥ 1/100 to < 1/10**	**Uncommon** ≥ 1/1,000 to < 1/100	**Rare** ≥ 1/10,000 to < 1/1,000	**Very Rare** < 1/10,000	**Frequency not known (cannot be estimated from the available data)**
Infections and Infestations		Mycotic superinfections, Candida infections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocythaemia	Haemolitic anaemia, Agranulocytosis Pancytopenia (life-threatening) Bone Marrow suppression (life threatening)	
Immune System Disorders			Allergic reaction, Allergic oedema / anngiooedema	Anaphylatic reaction, Anaphylacctic shock (life-threatening) (see section 4.4) Serum sickness-like reaction	
Endocrine Disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section

					4.4)
Psychiatric Disorders*		Psychomotor / hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicidal attempts and completed suicide) (see section 4.4) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicidal attempts and completed suicide) (see section 4.4)	Mania, incl. hypo mania
Nervous System Disorders*		Headache, Dizziness, Sleep disorders Taste disorders (*usuallyreversibleupon discontinuation of treatment)*	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (incl. status epilepticus see section 4.4) Vertigo Somnolence	Migraine Disturbed coordination Gait disturbance Smell disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and polyneuropathy (see section 4.4) Hyperaesthesia
Eye Disorders*			Visual disturbances (e.g. diplopia Peripheral neuropathy and polyneuropathy (see section 4.4)	Visual colour Distortions	
Ear and Labyrinth Disorders*			Tinnitus Hearing loss/ Hearing impaired		
Cardiac Disorders			Tachycardia		Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolo

					nged (see section 4.4 and 4.9)
Vascular Disorders			Vasodilation, Hypotension, Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (*includingasthmaticcondition*)		
Gastro-intestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pain Dyspepsia Flatulence	Dysphagia, Antibiotic associated colitis (*very rarely associated with possible fatal outcome, see section 4.4*)	Pancreatitis	
Hepatobiliary Disorders		Transient increase in transaminases Increased bilirubin	Transient hepatic impairment Cholestatic icterus Jaundice Hepatitis	Liver necrosis (*veryrarelyprogressing tolife-threateninghepatic failure*) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions (see section 4.4) Unspecific blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalised exanthematous pustulosis (AGEP) Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Musculoskeletal and Connective Tissue Disorders *		Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis Tendon rupture (*predominantlyAchillestendon)* (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*		Asthenia Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)		

Investigations		Transient increase in blood alkaline phosphatase	Prothrombin level abnormal Increased amylase		International normalised ratio increased (in patients with vitamin K antagonists)

*Very rare 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 tendonitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders, 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).

Paediatric population
The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Symptoms
An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.

Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria. Reversible renal toxicity has been reported.

Management
Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients must be kept well hydrated. Calcium or magnesium antacids may be administered as soon as possible after ingestion of Truoxin Tablets in order to reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.

In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

Pharmacokinetic/pharmacodynamic relationship:
Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:
In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All *in-vitro* mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in *Pseudomonas aeruginosa*) and efflux mechanisms may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST Recommendations

Microorganisms	**Susceptible**	**Resistant**
Enterobacteriaceae	S ≤ 0.25 mg/L	R > 0.5 mg/L
Salmonella spp	S ≤ 0.06 mg/L	R > 0.06 mg/L
Pseudomonas spp.	S ≤ 0.5 mg/L	R > 0.5 mg/L
Acinetobacter spp.	S ≤ 1 mg/L	R > 1 mg/L
Staphylococcus spp. 1	S ≤ 1 mg/L	R > 1 mg/L
Haemophilus influenzae	S ≤ 0.06 mg/L	R > 0.06 mg/L
Moraxella catarrhalis	S ≤ 0.125 mg/L	R > 0.125 mg/L
Neisseria gonorrhoeae	S ≤ 0.03 mg/L	R > 0.06 mg/L
Neisseria meningitidis	S ≤ 0.03 mg/L	R > 0.03 mg/L
Non-species-related breakpoints*	S ≤ 0.25 mg/L	R > 0.5 mg/L
1 Staphylococcus spp. - breakpoints for ciprofloxacin relate to high dose therapy. * Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.		

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms
Bacillus anthracis (1)
Aerobic Gram-negative micro-organisms

Aeromonas spp.
Brucella spp
Citrobacter koseri
Francisella tularensis
Haemophilus ducreyi
*Haemophilus influenzae**
Legionella spp.
*Moraxella catarrhalis**
Neisseria meningitidis
Pasteurella spp.
*Salmonella spp.**
*Shigella spp.**
Vibrio spp
Yersinia pestis
Anaerobic micro-organisms
Mobiluncus
Other micro-organisms
Chlamydia trachomatis ($)
Chlamydia pneumoniae ($)
Mycoplasma hominis ($)
Mycoplasma pneumoniae ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms
Enterococcus faecalis ($)
*Staphylococcus spp. *(2)*
Aerobic Gram-negative micro-organisms
Acinetobacter baumannii+
*Burkholderia cepacia+ **
*Campylobacter spp.+ **
*Citrobacter freundii**
Enterobacter aerogenes
*Enterobacter cloacae**
*Escherichia coli**
Klebsiella oxytoca
*Klebsiella pneumoniae**
*Morganella morganii**
*Neisseria gonorrhoeae**
*Proteus mirabilis**
*Proteus vulgaris**
Providencia spp.
*Pseudomonas aeruginosa**
Pseudomonas fluorescens
*Serratia marcescens**
Anaerobic micro-organisms
Peptostreptococcus spp.
Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms
Actinomyces
Enteroccus faecium
Listeria monocytogenes
Aerobic Gram-negative micro-organisms
Stenotrophomonas maltophilia
Anaerobic micro-organisms
Excepted as listed above
Other micro-organisms
Mycoplasma genitalium

Ureaplasma urealitycum

** Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications*
+ Resistance rate ≥50%in one or more EU countries
(\$): *Natural intermediate susceptibility in the absence of acquired mechanism of resistance*
(1) Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on in-vitro susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500 mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and/or international consensus documents regarding treatment of anthrax.
(2) Methicillin-resistant S. aureus very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. Single doses of 100-750 mg produced dose-dependent maximum serum concentrations (Cmax) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg. The absolute bioavailability is approximately 70-80%. A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution
Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Biotransformation
Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). The metabolites display in-vitro antimicrobial activity but to a lower degree than the parent compound. Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 iso-enzymes.

Elimination
Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. The serum elimination half-life in subjects with normal renal function is approximately 4-7 hours.

Excretion of ciprofloxacin (% of dose)		
	Oral Administration	
	Urine	**Faeces**
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half lives of ciprofloxacin of up to 12 h.

Non-renal clearance of ciprofloxacin is mainly due to active trans-intestinal secretion and metabolism. 1% of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

Paediatric patients

The pharmacokinetic data in paediatric patients are limited.

In a study in children C_{max} and AUC were not age-dependent (above one year of age). No notable increase in C_{max} and AUC upon multiple dosing (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

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 are observed. Crystalluria was noted in those species of animals which had normal 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.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity / photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin *in-vitro* and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability:
As reported for other gyrase inhibitors, ciprofloxacin causes damage to the weight-bearing joints of only juvenile rats and dogs treated with ciprofloxacin in repeat dose toxicity testing. This was more noticeable in the dog. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months. 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

5 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, 20, 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

Fannin Limited
Fannin House
South County Business Park
Leopardstown
Dublin 18
Ireland

8 MARKETING AUTHORISATION NUMBER

PA1457/013/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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