

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Ciprofloxacin 750mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 873mg ciprofloxacin hydrochloride equivalent to 750mg

Ciprofloxacin (INN)

For Excipients see section 6.1

3 PHARMACEUTICAL FORM

Coated tablet

Off-white capsule shaped biconvex film coated tablet

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults:

Ciprofloxacin is indicated for the treatment of the following infections when caused by ciprofloxacin-susceptible pathogens:

- Respiratory tract infections. Ciprofloxacin may be indicated for treating pneumonia due to gram-negative pathogens. In pneumococcal pneumonia treated in an outpatient setting, Ciprofloxacin is not the drug of first choice.
- Urinary tract infections: acute uncomplicated cystitis, complicated infections and pyelonephritis
- Infections of the genital organs including acute uncomplicated gonorrhoea, prostatitis
- Severe gastro-enteritis
- Skin and soft tissue infections
- Infections of the bones and joints
- Severe systemic infections: septicæmia, peritonitis, and infections in immunosuppressed patients.
- Intra-abdominal infections: intra-abdominal abscess
- Infections of the biliary tract : cholangitis, cholecystitis, empyema of the gall bladder
- Pelvic infections : salpingitis, endometritis, pelvic inflammatory disease

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

Children and adolescents:

Ciprofloxacin is indicated for the treatment of acute pulmonary exacerbation of cystic fibrosis in children and adolescents (5-17 years) caused by *Pseudomonas aeruginosa*. Ciprofloxacin is not recommended for other indications in this age group.

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

4.2 Posology and method of administration

Posology

The dose 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.

The duration of treatment depends on the severity of the disorder and on the clinical and bacteriological course. In principle, treatment should be maintained for at least 3 days after body temperature has returned to normal, or clinical symptoms have resolved.

Treatment may be initiated with tablets or intravenous injection according to the condition of the patient.

The following dose recommendations are provided as a guideline and refer to oral dosing only. (Note that different dose recommendations apply to intravenous administration of ciprofloxacin).

Adults: the dosage range for adults is 100-750 mg twice daily.

| Indication | Recommended Dosage |
|---------------------------------|--|
| Respiratory tract infections | 250-500 mg twice daily Usual duration of treatment: 7-14 days |
| Urinary tract infections | Acute, uncomplicated cystitis in women: 100-250 mg twice daily for 3 days Complicated infections and pyelonephritis: 250-500 mg twice daily. Usual duration of treatment: 7-14 days |
| Prostatitis | 500 mg twice daily. Usual duration of treatment: up to 28 days |
| Gonorrhoea | Acute uncomplicated 250-500 mg as a single dose |
| Severe gastro-enteritis | 500 mg twice daily. Usual duration of treatment: 3-7 days |
| Skin and soft tissue infections | 500 mg twice daily. Usual duration of treatment 5-10 days |
| Bone and joint infections | 500-750 mg twice daily. Usual duration of treatment 4-6 weeks or longer |
| Severe systemic infections | 500-750 mg twice daily. |

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| | In particularly severe, life-threatening infections - especially those involving <i>Pseudomonas</i> , staphylococci or streptococci, e.g. osteomyelitis, septicaemia, pneumococcal pneumonia, recurrent bouts of infection in mucoviscidosis patients, bone and joint infections or peritonitis - the recommended dose is 750 mg ciprofloxacin twice daily |
| Elective upper gastro-intestinal surgical and endoscopic procedures | 750 mg single dose 60-90 minutes prior to the procedure. If gastro-intestinal obstructive lesions are suspected, use with an anti-infective effective against anaerobes |
| Other indications | 500 - 750 mg twice a day |

Elderly patients:

Elderly patients should receive a dose depending on the severity of the disorder and on creatinine clearance.

Children and adolescents (5-17 years)

Acute pulmonary exacerbation of cystic fibrosis caused by *Pseudomonas aeruginosa*: 40 mg/kg/24 h, divided in two doses i.e. 20 mg/kg twice daily (maximum 1500 mg daily). Usual duration of treatment: 10-14 days.

Impaired renal function (recommendations apply to adults only):

| Creatinine clearance | Serum creatinine | Dose |
|---------------------------------|------------------------------------|-----------------------------|
| 31-60 mL/min/1.73m ² | 120-170 µmol (1.4 to 1.9 mg/dL) | Maximum dose 1000 mg/day |
| ≤ 30 mL/min/1.73m ² | ≥175 µmol (≥ 2.0 mg/dL) | Maximum dose 500 mg/day* |

* In patients with severe infections and severe renal impairment, a unit dose of 750 mg can be given. However, patients should be carefully monitored. Dosage intervals should remain the same as in patients with normal renal function.

Impaired renal function + haemodialysis

Recommended dose: 500 mg per day administered as a single dose following haemodialysis..

Impaired renal function + continuous ambulatory peritoneal dialysis (CAPD)

Recommended dose: 500 mg per day administered as a single dose following CAPD.

Impaired hepatic function

Dose adjustment is not necessary in mild or moderate hepatic failure but may be considered necessary in severe hepatic failure.

Impaired renal and hepatic function:

Dose adjustment as under impaired renal function.

Children and adolescents (5-17 years):

Dosage in children with reduced renal and liver function has not been investigated.

Method of administration:

The tablets are to be swallowed with liquid. They can be taken at any time regardless of meals. Ingestion on an empty stomach accelerates the absorption of active substance. Dairy products with a high calcium content (milk, yoghurt) may reduce ciprofloxacin absorption (see section 4.5).

4.3 Contra-Indications

Ciprofloxacin is contraindicated in:

- Patients with a history of hypersensitivity to ciprofloxacin, to any other fluoroquinolone or to any of the other ingredients in ciprofloxacin tablets listed in section 6.1.
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5)

4.4 Special Warnings and special precautions for use

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

Ciprofloxacin monotherapy is not suitable 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.

Genital tract infections

Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates.

Therefore, ciprofloxacin should be administered for the treatment of gonococcal urethritis 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.

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).

Broncho-pulmonary infections in cystic fibrosis

Clinical trials have included children and adolescents aged 5 to 17 years. More limited experience is available in treating children between 1 and 5 years of age.

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 to 17 years.

Other specific severe infections

Treatment of other severe infections should be 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 a 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 following a single dose (see section 4.8) and may be life-threatening. If such reaction occurs, ciprofloxacin 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 standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.

Tendinitis and tendon rupture (especially Achilles tendon), sometimes bilateral, may occur due to ciprofloxacin use, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin therapy. The risk of tendinopathy may be

increased in elderly patients or in patients concomitantly treated with corticosteroids (see section 4.8). At any sign of (e.g. painful swelling, inflammation), ciprofloxacin treatment should be discontinued. Care should be taken to keep the affected limb at rest.

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

Vision disorders:

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

Photosensitivity

Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should avoid direct exposure to either extensive sunlight or UV irradiation during treatment.

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 predispose to seizure. If seizures occur, ciprofloxacin should be discontinued.

Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, treatment should be discontinued (see section 4.8).

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, alone or in combination, 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 tablets, 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 tablets, in these populations.

(See section 4.2 Elderly, section 4.5, section 4.8, section 4.9)

Hypoglycaemia:

As with other quinolones, hypoglycaemia has been reported most often in diabetic patients, predominantly in the elderly population. In all diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Gastrointestinal system

The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases ciprofloxacin should be immediately discontinued and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.

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

Since ciprofloxacin is largely excreted unchanged via renal pathway 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-phosphate dehydrogenase deficiency

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. 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 CYP 1A2 and thus may cause increased serum concentrations 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).

Interaction with laboratory tests

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

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

4.5 Interactions with other medicinal products and other forms of interaction

Effects of other products on ciprofloxacin

Drugs known to prolong QT interval

Ciprofloxacin tablets, 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. magnesium, aluminium or calcium), 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 to 2 hours before or at least 4 hours after these preparations. This restriction does not apply to antacids belonging to the class of H₂-receptor blockers.

Food and Dairy Products

Dietary calcium as part of a meal does not significantly affect absorption. However, 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.

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin (oral) 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 C_{max} 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 clinical study with healthy subjects, there was an increase in serum tizanidine concentration (C_{max} increase 7-fold, range 4 to 21-fold; AUC increase 10-fold, range 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended (see section 4.4).

Theophylline

Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to

theophylline-induced side effects that may rarely be life threatening or fatal. During the combination serum theophylline concentrations should be checked and the theophylline dose reduced as necessary (see section 4.4).

Other xanthine derivatives

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

Phenytoin

Simultaneous administration of ciprofloxacin and phenytoin may result in increased or reduced serum levels of phenytoin such that monitoring of drug levels is recommended.

Ciclosporin

A transient rise in the concentration of serum creatinine is seen when ciprofloxacin and ciclosporin containing medicinal products were administered simultaneously. Therefore it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

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 C_{max} 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 CYP450 1A2 isozyme, results in an increase of C_{max} 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-desmethylozapine 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

C_{max} 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.

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 'Special warnings and precautions for use').

Zolpidem

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

4.6 Pregnancy and Lactation

Pregnancy

The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or fetoneonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. 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).

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

Breast-feeding

Ciprofloxacin is excreted 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 Machine

Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

4.1. Undesirable Effects

Adverse reactions are listed by frequency: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $\leq 1/100$); rare ($\geq 1/10,000$ to $\leq 1/1,000$); very rare ($\leq 1/10,000$).

The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.

| System Organ Class | Common $\geq 1/100$ to $< 1/10$ | Uncommon $\geq 1/1,000$ to $< 1/100$ | Rare $\geq 1/10,000$ to $< 1/1,000$ | Very Rare $< 1/10,000$ | Frequency known (cannot be estimated: the available data) |
|--------------------------------------|------------------------------------|---|--|---|---|
| Infections and Infestations | | Mycotic superinfections | | | |
| Blood and Lymphatic System Disorders | | Eosinophilia | Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytosis | Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening) | |
| Immune System Disorders | | | Allergic reaction Allergic oedema / angiooedema | Anaphylactic reaction Anaphylactic shock (life-threatening) (see section 4.4) Serum sickness-like reaction | |
| Metabolism and Nutrition Disorders | | Decreased appetite | Hyperglycaemia Hypoglycaemia (see section 4.4) | | |
| Psychiatric Disorders | | Psychomotor hyperactivity / agitation | Confusion and disorientation Anxiety reaction Abnormal dreams | Psychotic reactions (potentially culminating in | Mania Hypomani |

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|---|---------------------|---|---|--|---|
| | | | Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations | suicidal ideations/ thoughts or suicide attempts and completed suicide) (see section 4.4) | |
| Nervous System Disorders | | Headache Dizziness Sleep disorders Taste disorders | Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus see section 4.4) Vertigo | Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri | Peripheral neuropathy; polyneuropathy (see section 4.4) |
| Eye Disorders | | | Visual disturbances (e.g. diplopia) | Visual colour distortions | |
| Ear and Labyrinth Disorders | | | Tinnitus Hearing loss / Hearing impaired | | |
| Cardiac Disorders | | | Tachycardia | | Ventricular arrhythmias and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation) (see sections 4.8 and 4.9) |
| Vascular Disorders | | | Vasodilatation Hypotension Syncope | Vasculitis | |
| Respiratory, Thoracic and Mediastinal Disorders | | | Dyspnoea (including asthmatic condition) | | |
| Gastro-intestinal Disorders | Nausea Diarrhoea | Vomiting Gastrointestinal | Antibiotic associated | Pancreatitis | |

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|--|--|---|---|--|--|
| | | and abdominal pains Dyspepsia Flatulence | diarrhoea, including pseudomembranous colitis (very rarely with possible fatal outcome) (see section 4.4) | | |
| Hepatobiliary Disorders | | Increase in transaminases Increased bilirubin | Hepatic impairment Cholestatic icterus Hepatitis | Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4) | |
| Skin and Subcutaneous Tissue Disorders | | Rash Pruritus Urticaria | Photosensitivity reactions (see section 4.4) | Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening) | Acute generalised exanthematous pustulosis (AGEP) DRESS |
| Musculo-skeletal and Connective Tissue Disorders | | Musculoskeletal pain (e.g. extremity pain, back pain, chest pain) Arthralgia | Myalgia Arthritis Increased muscle tone and cramping | Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (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 Fever | Oedema Sweating (hyperhidrosis) | | |

| | | | | | |
|----------------|--|--|-------------------|--|--|
| Investigations | | Increase in blood alkaline phosphatase | Increased amylase | | International normalised ratio increase (in patient treated with Vitamin K antagonist) |
|----------------|--|--|-------------------|--|--|

The incidence of arthropathy, 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

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

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 should be kept well hydrated. Calcium or magnesium containing antacids may theoretically 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.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: J01M A02

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 (C_{max}) 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 ≤ 0.5 mg/L | R > 1 mg/L |
| <i>Pseudomonas</i> spp | S ≤ 0.5 mg/L | R > 1 mg/L |
| <i>Acinetobacter</i> spp | S ≤ 1 mg/L | R > 1 mg/L |
| <i>Staphylococcus</i> spp.1 | S ≤ 1 mg/L | R > 1 mg/L |
| <i>Haemophilus influenzae</i> and <i>Moraxella catarrhalis</i> | S ≤ 0.5 mg/L | R > 0.5 mg/L |
| <i>Neisseria gonorrhoeae</i> | S ≤ 0.03 mg/L | R > 0.06 mg/L |
| <i>Neisseria meningitidis</i> | S ≤ 0.03 mg/L | R > 0.06 mg/L |
| Non-species-related breakpoints* | S ≤ 0.5 mg/L | R > 1 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 Enterococcus 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 $\geq 50\%$ 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 adult 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 (C_{max}) 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 (M1-M4) | 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

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

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 large weight-bearing joints in immature animals. 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains

Tablet core

lactose monohydrate,
sodium starch glycollate,
povidone,
sodium stearyl fumarate,

Tablet coating

methocel,
polyethylene glycol 400
titanium dioxide.

6.2 Incompatibilities

Not applicable

6.3. Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

PVC-Aluminium blister strips in cartons containing 10 or 100 tablets

6.6 Special precautions for disposal

Not applicable

7. MARKETING AUTHORISATION HOLDER

Strides Pharma UK Ltd
Unit 4 Metro Centre
Tolpits Lane
Watford
Hertfordshire
WD18 9SS
Trading as: Co-pharma

8 MARKETING AUTHORISATION NUMBER(S)

PL 13606/0142

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10 DATE OF REVISION OF THE TEXT

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