MECURE INDUSTRIES PLC

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

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1. Name of the Medicinal Product

ZYPROX TABLETS

2. Qualitative and Quantitative Composition

Ciprofloxacin 500 mg, film-coated tablets

1 film-coated tablet contains: 500 mg Ciprofloxacin (as Ciprofloxacin Hydrochloride)

For excipients see 6.1

3. Pharmaceutical Form

Film-coated tablet

White caplet shaped oblong film coated tablets, having embossed with "ZYPROX "on one side and on the other side is "500 ".

4. Clinical Particulars

4.1. Therapeutic Indications

Adults:

Treatment of infections caused by ciprofloxacin-sensitive pathogens, such as:

- Infections of the respiratory tract. 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,
- Infections of the urinary tract: acute uncomplicated cystitis, complicated infections and pyelonephritis;
- Infections of the genital organs, including acute, uncomplicated gonorrhoea, prostatitis
- Severe bacterial enteritis;
- Severe skin and soft tissue caused by Gram-negative bacteria;
- Osteomyelitis caused by Gram-negative bacteria;
- Severe systemic infections caused by Gram-negative bacteria: e.g. septicaemia, peritonitis (in case of peritonitis, the anaerobic compartment should be covered by another antibacterial agent (metronidazole like), infections in immuno-suppressed patients.

Children and adolescents:

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

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

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 dose range for adults is 250 - 750 mg twice daily.

Respiratory tract infections:

250-500 mg twice daily

Usual duration of treatment: 7-14 days

Urinary tract infections:

- acute, uncomplicated cystitis in women: 250 mg twice daily for three days. Usual duration of treatment: 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. Usual duration of treatment: Single dose.

Severe bacterial 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

Osteomyelitis:

500 mg twice daily. Usual duration of treatment 4 to 6 weeks or longer

Severe systemic infections:

500-750 mg twice daily

In particularly severe, life-threatening infections – especially those involving Pseudomonas, staphylococci or streptococci, e. g. osteomyelitis, septicaemia, streptococcal pneumonia, recurrent bouts of infection in mucoviscidosis patients, severe skin and soft tissue infections or peritonitis – the recommended dose is 750 mg ciprofloxacin twice daily.

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.

Other indications: Not recommended.

Impaired renal or hepatic function

Adults:

1. *Impaired renal function*

   Creatinine clearance: 31 to 60 ml/min/1.73 m^2 (Serum creatinine level: 120-170 µmol/l (1.4-1.9 mg/dl): Maximum dose 1000 mg per day

   Creatinine clearance ≤ 30 ml/min/1.73 m^2 (Serum creatinine level ≥ 175 µmol/l (≥ 2.0 mg/dl): Maximum dose 500 mg* per 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. Monitoring of

drug levels in blood provides the most reliable basis for dose adjustment. Dosage intervals should remain the same as in patients with normal renal function.

2. *Impaired renal function and haemodialysis*
   Recommended dose: 500 mg per day administered as a single dose following haemodialysis. Monitoring of drug levels in blood provides the most reliable basis for dose adjustment.
3. *Impaired renal function and continuos ambulatory peritoneal dialysis (CAPD)*
   Recommended dose: 500 mg per day administered as a single dose following CAPD. Monitoring of drug levels in blood provides the most reliable basis for dose adjustment.

Impaired hepatic function
Dose adjustment is not necessary in mild or moderate hepatic failure but may be necessary in severe hepatic failure. Monitoring of drug levels in blood provides the most reliable basis for dose adjustment."
Impaired renal and hepatic function
Dose adjustment as any under 1, with monitoring of serum ciprofloxacin concentrations.
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 accelerate the absorption of active substance. Dairy products with a high calcium content (milk, yoghurt) may reduce ciprofloxacin absorption.

4.3. Contra-Indications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).
- Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

4.4. Special warnings and precautions for use

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.

The use of Ciprofloxacin 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 Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment (see also section 4.3).

<u>Severe infections and mixed infections with Gram-positive and anaerobic pathogens</u>

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.

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 uretritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should 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.

Travelers' diarrhea

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 5-17 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 1-17 years.

Other specific severe infections

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.

<u>Hypersensitivity</u>

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.

<u>Musculoskeletal System</u>

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.

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

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be aggravated (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 be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment (see section 4.8).

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 may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thought culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.

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

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 immediately be 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 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).

Interaction with tests

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

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] 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)

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. [INN] 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.

4.5. Interaction with other medicinal products and other forms of interaction

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

Antacids, iron, zinc, sucralfate, calcium, didanosine, oral nutritional solutions, dairy products

Absorption of ciprofloxacin is reduced when iron, sucralfate or antacids and highly buffered pharmaceuticals, containing magnesium, aluminium or calcium, are administered simultaneously. This also applies to sucralfate, antiviral drugs containing buffered didanosine formulations, oral nutritional solutions and large quantities of dairy products (milk or liquid milk products such as yoghurt). Therefore ciprofloxacin should be administered either 1 to 2

hours before or at least 4 hours after the above mentioned products. This restriction does not apply to the group of H_2 receptor-blocking antacids.

Xanthine derivatives

Concurrent administration of ciprofloxacin and theophylline may cause increased plasma concentrations of theophylline. This may lead to theophylline induced undesirable effects, which in very rare cases are life-threatening. During concurrent administration of theophylline the plasma concentrations should be monitored and the theophylline dose should be adjusted adequately. On concurrent administration of ciprofloxacin and caffeine or pentoxifylline, raised serum concentrations of these xanthine derivatives were reported.

NSAIDs

Animal trials have shown that concurrent administration of very high doses of a quinolone and certain non steroid anti-inflammatory drugs (NSAIDs) (but not acetylsalicylic acid) may provoke convulsions.

Cyclosporin

A transient increase in the concentration of plasma creatinine is seen when ciprofloxacin and cyclosporin are administered simultaneously. Plasma creatinine concentrations should be checked regularly in these patients.

Oral anticoagulants

Ciprofloxacin, like other quinolones, may enhance the effect of coumarin derivatives including warfarin. In the case of concomitant administration of these products, prothrombin time (PT) or other suitable coagulation tests should be monitored. If necessary, the oral anticoagulant dosage should be adjusted as appropriate.

Glibenclamide

Simultaneous administration of ciprofloxacin and glibenclamide may increase the effect of glibenclamide.

Probenecid

Probenecid inhibits the renal excretion of ciprofloxacin resulting in an increase of the plasma concentration of ciprofloxacin.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin. The maximum plasma concentration is therefore achieved more rapidly. The bioavailability of ciprofloxacin is not affected.

Mexiletine

Simultaneous administration of ciprofloxacin and mexiletine can lead to increased plasma concentrations of mexiletine.

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.

Premedicants

It is recommended that opiate premedicants, (e.g. papaveretum) or opiate premedicants used with anticholinergic premedicants, (e.g. atropine or hyoscine) are not used concomitantly with ciprofloxacin, as the serum levels of ciprofloxacin are reduced.

Co-administration of ciprofloxacin and benzodiazepine premedicants has been shown not to affect ciprofloxacin plasma levels. However, since decreased clearance of diazepam with a prolonged half-life has been reported during co-administration of ciprofloxacin and diazepam, and in an isolated case with midazolam, careful monitoring of benzodiazepine therapy is recommended.

Ropinirole
A potential for increased plasma levels of ropinirole with possible increase in adverse effects exists. In case of combined use, increased clinical monitoring and dosage adjustment of ropinirole may be required.
Buffered didanosine formulations
Clinically important interactions have been reported with buffered didanosine formulations (refer to the first paragraph of this section).
Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

4.6. Pregnancy and Lactation

(Refer to section 4.3)
Use during pregnancy is contraindicated. As with other quinolones, ciprofloxacin has been shown to cause arthropathy in immature animals, and therefore its use during pregnancy is contraindicated.
Administration to nursing mothers is contraindicated since quinolones administrated at therapeutic doses are excreted in breast-milk in quantities that can be expected to affect the infant.

4.7. Effects on the ability to drive and use machines

Even when used as prescribed, this medicinal product can alter the capacity for reactions to an extent that impairs the ability to take an active part in road traffic, to operate machinery or to work safely. This applies to a greater degree at the start of treatment, when the dose is increased, and when switching medication, as well as in conjunction with alcohol.

4.8. Undesirable effects

Adverse effects have been reported in 5-14% of patients receiving ciprofloxacin. Most frequent adverse effects of the drug involve the gastro-intestinal tract and the central nervous system.
The following undesirable effects have been observed:
Infections and infestations
Long-term and repeated use of ciprofloxacin can lead to superinfections with resistant bacteria or fungi.
Blood and lymphatic system disorders
Uncommon (≥1/1.000, <1/100): eosinophilia, leucopenia, granulocytopenia, anaemia, thrombocytopenia.
Very rare (<1/10.000): leucocytosis, thrombocytosis, haemolytic anaemia, pancytopenia, agranulocytosis, altered prothrombin values.
Immune system disorders
The following reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately and the treating physician informed.
Common (≥1/100, <1/10): Skin reactions such as rash, pruritus, drug fever.
Very rare (<1/10.000): punctiform cutaneous bleeding (petechiae), vesicles with haemorrhage (haemorrhagic bullae) and small nodules (papules) with crust formation showing vascular

involvement (vasculitis), urticaria, erythema nodosum, erythema multiforme (mild to very severe forms i.e. Stevens-Johnson syndrome), Lyell syndrome.
Interstitial nephritis, hepatitis, and hepatic necrosis to life-threatening hepatic failure.
Anaphylactic/anaphylactoid reactions (e.g. ranging from facial, vascular and laryngeal oedema, through dyspnoea to shock), in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately, and medical treatment for shock should be given.
Metabolism and nutrition disorders
Common (≥1/100, <1/10): loss of appetite.
Very rare (<1/10.000): hyperglycaemia.
Psychiatric disorders
Common (≥1/100, <1/10): tiredness, agitation, confusion.
Very rare (<1/10.000): insomnia, anxiety states, nightmares, distress, depression, hallucinations.
Psychotic reactions (involving in some cases a risk of self-injury): these reactions occurred in some cases with the first dose of the medicinal product. If such reactions occur, ciprofloxacin is to be discontinued immediately and the treating physician informed.
Depression and psychotic reactions may result in and have been observed with self-endangering behaviour. See section 4.4.
Nervous system disorders
Common (≥1/100, <1/10): dizziness, headache, tremor.
Very rare (<1/10.000): paraesthesia, ataxia, convulsive seizures (the spasmodic threshold in epilepsy may be reduced), increased intracranial pressure, migraine, fainting, aggravation of the symptoms of myasthenia; dysgeusia and dysosmia as well as a possible loss of the sense of smell, which normally recovers after the end of the therapy.
Eye disorders
Very rare (<1/10.000): disturbed vision (e.g. diplopia, chromatopsia).
Ear and labyrinth disorders
Very rare (<1/10.000): tinnitus, transient (especially high-frequency) hearing loss.
Cardiac disorders
Uncommon (≥1/100, <1/10): palpitation
Very rare (< 1/10000): syncope, tachycardia, ventricular arrhythmia*, torsades de pointes*, QT prolongation*
*These events were observed predominantly among patients with further risk factors for QTc prolongation.
Vascular disorders
Very rare (<1/10.000): hot flushes, hypertension.
Respiratory, thoracic and mediastinal disorders
Uncommon (>1/1.000, <1/100): pulmonary embolism, dyspnoea, pulmonary oedema, epistaxis, haemoptysis and hiccough.
Gastrointestinal disorders
Common (≥1/100, <1/10): nausea, diarrhoea, vomiting, digestive disorders, abdominal pain, flatulence.
Rare (≥1/10.000, <1/1.000): pseudomembranous colitis.
Very rare (<1/10.000): pancreatitis.
Skin and subcutaneous tissue disorders
Very rare (<1/10.000): photosensitivity: it is recommended that patients avoid long lasting exposure to sunlight or irradiation with UV-light (solarium) during treatment with

ciprofloxacin; treatment should be discontinued in cases of photosensitivity reactions (e.g. skin reactions similar to sun burn). Sweating.
Musculoskeletal and connective tissue disorders
Uncommon (≥1/1.000, <1/100): arthralgia and joint swelling.
Very rare (<1/10.000): muscular pains, inflammation of tendon sheaths (tenosynovitis).
In isolated cases, tendinitis and torn tendons (e.g. of Achilles' tendon) may occur during treatment with fluoroquinolones. These events were observed predominantly among older patients who had been systemically treated beforehand with corticosteroids. If tendinitis is suspected, treatment with ciprofloxacin must be discontinued immediately, physical effort avoided and, if necessary, medical treatment initiated.
Renal and urinary disorders
Very rare (<1/10.000): transient impairment of kidney function to transient renal failure, crystalluria or haematuria.
General disorders and administration site conditions
Very rare (<1/10.000): peripheral oedema, asthenia.
Investigations
Patients with liver damage in particular may show a transient rise in transaminases and alkaline phosphatase or even cholestatic jaundice; a transient increase in serum urea, creatinine or bilirubine.

4.9. Overdose

Toxicity: There is limited experience on overdose, but ciprofloxacin is considered to be of low toxicity.
Symptoms: Dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion. Gastrointestinal upset, liver and kidney abnormalities. Crystalluria, haematuria.
Treatment: In acute overdosage, reversible kidney damage is seen. Gastric emptying by eliciting vomiting or gastric lavage is therefore recommended. Activated charcoal, Mg- or Ca-containing antacids are administered in order to reduce the absorption of ciprofloxacin. The patient should be kept under accurate observation receiving both symptomatic and supportive treatment. The renal function should be monitored. At haemodialysis or peritoneal dialysis only a modest amount of ciprofloxacin (<10%) is eliminated. Adequate hydration must be maintained to minimise the risk of crystalluria.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Therapeutic classification: J 01 MA 02

Activity:

Ciprofloxacin is a synthetic 4-quinolone derivative antibacterial agent of the fluoroquinolone class.

Mechanism of action:

As a fluoroquinolone antibacterial agent, ciprofloxacin acts on the DNA-DNA-gyrase complex and topoisomerase IV.

Spectrum of activity:

Breakpoints:

BSAC: S[1ml/L; Rμ 2mg/l, except Pseudomonas R μ 8mg/ml and UTI R μ 8mg/L.

NCCLS: S [1mg/1; I = 2mg/l; R µ 4mg/l.

Susceptibility

The prevalence of the acquired resistances can vary for some species geographically and with time. Therefore, it is important to obtain information on local resistance patterns, particularly when treating more severe infections.

The information provided below gives only an approximate guidance on probabilities whether micro-organisms will be susceptible to ciprofloxacin or not.

Organism	**Prevalence of Resistance**
Sensitive:	
Gram-positive bacteria	
Staphylococcus aureus (methicillin sensitive)	0-14%
Streptococcus agalactiae	0-17%
Gram-negative bacteria	
Acinetobacter baumanii	6-93%
Acinetobacter spp.	14-70%
Aeromonas hydrophila	
Campylobacter jejuni/coli	0-82%
Citrobacter freundii	0-4%
Enterobacter aerogenes	
Enterobacter cloacae	0-3%
Enterobacter spp	3-13%
Escherichia coli	2-7%
Haemophilus influenzae	0-1%
Klebsiella spp.	2-21%
Moraxella catarrhalis	
Morganella morganii	1-2%
Neisseria gonorrhoeae	5%
Plesiomonas shigelloides	
Proteus mirabilis	0-10%
Proteus vulgaris	4%
Providencia spp.	4%
Pseudomonas aeruginosa	1-28%
Salmonella spp.	
Salmonella typhi	0-2%
Serratia liquefaciens	
Serratia marcescens	23%
Shigella spp	

Vibrio spp	
Yersinia enterocolitica	
Anaerobes*	
Peptococcus spp.	-
Peptostreptococcus spp.	-
Veillonella parvula	-
Other pathogens	
Legionella pneumophila	-
Intermediate	
Viridans streptoeocci	5-9%
Streptococcus pneumonziae	2.8%
Streptococcus pyogenes	2.8%
Other pathogens	
Chlamydia spp	-
Resistant	
Gram-positive aerobes	
Enterococcus spp	-
Staphylococcus aureus (methicillin resistant)	48-90%
Gram-negative aerobes	
Stenotrophomonas maltophila	-
Flavobacterium menmgosepticum	-
Nocardia asteroides	-
Anaerobes	
Bacteroides_fragilis	-
Bacteroides thetaiotaomicron	-
Clostridium difficile	-

* Ciprofloxacin is not considered the drug of first choice for treatment of infections with anaerobes.

In-vitro investigations have shown that resistance to ciprofloxacin is commonly due to mutations in bacterial topoisomerases and usually develops slowly and gradually ("multiple-step" type).

Cross-resistance between fluoroquinolones may occur when the mechanism of resistance is due to mutations in bacterial gyrases. However, single mutations may not result in clinical resistance, but multiple mutations generally do result in clinical resistance to all drugs within the class. Impermeability and/or drug efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physicochemical properties of the various drugs within the class and the affinity of transport systems for each drug.

5.2 Pharmacokinetic properties

Absorption

After oral administration, ciprofloxacin is predominantly absorbed from the duodenum and upper jejunum, and reaches peak serum concentrations within 60-90 min. After single doses of 250mg and 500mg C_{max} values are about 0.8-2.0mg/1 and 1.5-2.9mg/1 respectively

The absolute bioavailability is approximately 70 to 80%. C_{max}- and AUC-values are proportionally increased with the dose.

Food intake has no effect on the plasma concentration profile of ciprofloxacin.

Distribution

The steady-state volume of distribution of ciprofloxacin is 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma in non-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravasal space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.

Metabolism / Elimination

Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5ml/min/kg, and total clearance amounts to 8-10ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.

Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 show antibacterial activity comparable with or smaller than nalidixic acid. M 4 with the lowest quantity, has an antimicrobial activity very much corresponding to norfloxacin.

Excretion after oral administration (in % of the ciproftoxacin dose):

	urine	faeces
Ciprofloxacin	44.7	25.0
Metabolites	11.3	7.5

The half-life of ciprofloxacin lies between 3 and 5 hours, both after oral and after intravenous administration.

Since ciprofloxacin is excreted not only via the kidneys, but also to a major extent via the gut, renal function must be substantially impaired before increases in serum elimination half-life of up to 12 hours are observed.

5.3 Preclinical safety data

Like other gyrase inhibitors, ciprofloxacin may induce joint damage during the growth phase of juvenile animals. Other preclinical effects were observed only at exposures, sufficiently in excess of the maximum human exposure, that make concern for human safety negligible in respect of animal data.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core:

Starch

P. V. P K30

Sodium Starch Glycolate

Sodium Lauryl Sulphate

Aerosil

Cross Carmellose Sodium

Magnesium Stearate

Talcum

Sodium Stearyl Fumarate

Film coating:

Isopropyl Alcohol

Tabcoat TC 2054* (White)

Methylene Chloride

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store in a cool dry place at temperature below 30°C. Store in the original packaging.

6.5 Nature and contents of container

Blister strips of 20 µm Aluminium and 250 µm PVC in a cardboard outer container. Pack sizes: 2 blisters of 7 tablets.

6.6 Special precautions for disposal and other handling

None.

7. Marketing authorization holder

Me Cure Industries Limited

Plot 6 Block H, Debo Industries Compound,

Oshodi Industrial Scheme,

Oshodi,

Lagos,

Nigeria.

8.0 NAFDAC Registration Number: 04-9612