SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

(CIPROLEX) Ciprofloxacin 500 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 film coated Ciprofloxacin 500 mg tablet contains: 500 mg ciprofloxacin (as hydrochloride)

For excipients see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablet.

Off white, capsule shaped, film coated tablets, debossed with 'CPX' and '500' on one side and UNICHEM on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

CIPROLEX tablets are indicated for the treatment of a variety of infections caused by susceptible gram-positive and gram negative organisms including mixed infections caused by two or more organisms. It may also be used for infections caused by multi-drug resistant bacteria. CIPROLEX is indicated for the treatment of the following infections caused by susceptible bacteria.

Respiratory Tract Infections:

Acute bronchitis, exacerbation of chronic obstructive airway disease, empyema, lung abscess, infected bronchiectasis, cystic fibrosis and pneumonia.

Urinary Tract Infections:

Acute and chronic pyelonephritis, prostatitis, systitis, epididymitis and chronic completed or recurrent UTI caused by multi-resistant organisms and or *Pseudomoonas aeruginosa*.

Skin and Soft tissue Infections:

In surgical and post operative wound infections due to gram-negative organisms such as Enterobacteriaceae and *Pseudomonas aeruginosa*. It is also useful in infections caused by *Staphilococci.*

Surgical Infections:

Peritonitis, intra abdominal abscess, cholangitis. cholecystitis, emphysema of gall bladder

Bone and Joint Infections:

Since CIPROLEX achieves adequate tissue concentrations in the bone, it is useful in the management of acute and chronic ostenmyelitis.

Gynaecological Infections:

Severe pelvic infections caused by susceptible bacteria.

Sexually Transmitted Diseases:

Gonorrhoea including that caused by beta-lactamase producing strains. Chancroid caused by *H. dureyi.*

Gastrointestinal Infections:

Effective in the treatment of typhoid and may also eradicate carrier stage. It is also useful in the treatment of resistant *Salmonella typhi* infections.

Severe Systemic Infections:

Septicemia, bacteremia, infections in immunocompromised patients.

4.2. Posology and method of administration

Posology

The dose of CIPROLEX 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. The duration of CIPROLEX therapy depends upon the type and severity of the infection and should be determined by the clinical and bacteriological response of the patients. For most infections, therapy should be continued for at least 48 hours after the patient becomes asymptomatic. The usual duration is 1-2 weeks but severe or complicated infections may require more prolonged therapy.

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:

Respiratory tract infections:

250-500 mg twice daily

Usual duration of treatment: 7-14 days

Urinary tract infections:

- acute, uncomplicated cystitis in women: 100 mg-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 unchewed 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 high calcium content (milk, yoghurt) may reduce ciprofloxacin absorption.

4.3. Contra-Indications

Ciprofloxacin must not be used in cases of hypersensitivity to ciprofloxacin or any of the excipients or other chemotherapeutic agents of the quinolone type.

Pregnancy, Lactation (refer to section 4.6).

In patients with a history of tendon disorders related to fluoroquinolone administration (refer to section 4.4).

Children and growing adolescents (5-17 years), contraindicated except for the treatment of acute pulmonary exacerbation of cystic fibrosis (refer to sections 4.2 and 4.4).

Children under 5 years.

4.4. Special warnings and precautions for use

Use in patients with epilepsy and other central nervous system (CNS) disorders:
In patients with epilepsy or other lesions of the central nervous system (e.g. reduced convulsion threshold, a history of seizures, diminished cerebral blood flow, changes in brain structure or stroke), ciprofloxacin is only to be used after carefully weighing the benefits against the risk, because the possibility of central nervous side effects puts these patients at increased risk.

Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided. Pseudomembranous colitis is a particular form of enterocolitis that can occur with antibiotics (in most cases due to *Clostridium difficile*). If severe and persistent diarrhoea occurs during or after treatment, the doctor should be consulted. Even if *Clostridium difficile* is only suspected, administration of ciprofloxacin should be discontinued immediately and appropriate treatment given.

Patients with a family history of or actual defects in glucose-6-phosphate dehydrogenase activity are prone to haemolytic reactions with quinolones, and so ciprofloxacin should be used with caution in these patients.

Ciprofloxacin use has rarely been associated with photosensitivity. However, patients should be recommended to avoid prolonged exposure to sunlight or UV radiation during treatment with ciprofloxacin. If this is not possible appropriate precautions should be taken.

Tendinitis and/or rupture of tendons (which mainly affects the Achilles tendon) are observed during treatment with quinolone antibiotics. These reactions are especially observed in elderly patients and patients treated with corticosteroids. After the first signs of pain or inflammation, the treatment should be discontinued and the affected extremity should be made non-weight bearing. If the symptoms originate from the Achilles tendon, care should be taken to avoid rupture of both tendons (i.e. by use of splints to both Achilles tendons or support of both heals) (refer to section 4.3).

Because ciprofloxacin has some activity against *Mycobacterium tuberculosis*, false-negative cultures may occur when specimens are obtained during ciprofloxacin treatment. Ciprofloxacin should be used with caution in patients with myasthenia gravis.

Studies in immature animals showed ciprofloxacin may cause arthropathy in weight-bearing joints. However, review of safety data in patients younger than 18 years (mainly cystic fibrosis patients) revealed no signs of drug related damage to cartilage or joints.

If failure of therapy is suspected in treatment of *Pseudomonas aeruginosa* or *Staphylococcus*, microbiological studies to identify resistant pathogens should be considered.

Since ciprofloxacin is associated with very rare cases of QT prolongation (see section 4.8) caution should be exercised when treating patients at risk for torsade de pointes arrhythmia."
Possible undesirable effects like depression and psychosis may result in and have been observed with self-endangering behaviour and treatment must be discontinued in these cases.

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): hyperglycemia.

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, and 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

Pharmacotherapeutic group: Quinolone antibacterials (ATC code: J01MA02)

Mode of action:

Ciprofloxacin is effective in vitro against a large number of Gram-negative aerobic bacteria including *P. aeruginosa*. It is also effective against Gram-positive organisms, such as staphylococci and streptococci. Anaerobes are generally less sensitive. Ciprofloxacin has a rapid bactericidal effect, both in the growth phase and in the rest phase. During the growth phase of bacteria, a partial rolling up and unfolding of chromosomes takes place. The enzyme DNA-gyrase plays a crucial role in this process. Ciprofloxacin inhibits DNA-gyrase, resulting in inhibition of DNA synthesis.

Mechanism of resistance:

Resistance to ciprofloxacin develops in stages through genomic mutations (multiple-step type). Transferable plasmid-mediated quinolone resistance associated with qnr has been detected in quinolone-resistant clinical strains of *E. coli* and *Klebsiella spp*. As a result of its mechanism of action, ciprofloxacin does not show cross-resistance with other important, chemically different groups of substances such as beta-lactam antibiotics, aminoglycosides, tetracyclines, macrolides and polypeptides, sulphonamides, trimethoprim and nitrofurantoine.

Within the class of quinolones cross-resistance has been observed. Development of resistance to ciprofloxacin and other fluoroquinolones has been observed in staphylococci; especially methicillin-resistant *S. aureus, P. aeruginosa, E. coli and E. faecalis* (see the right column in the sensitivity table).

Especially patients undergoing long-term treatment (e.g. in cystic fibrosis, osteomyelitis), or patients who are extremely susceptible to infections (e.g. in selective prophylaxis in certain groups of neutropenic patients, artificial ventilation) show the highest risk. The percentage of resistant strains can be subject to great local variation. Regular determination of resistance is therefore recommended.

Breakpoints:

According to EUCAST the following breakpoints for aerobic bacteria have been defined for ciprofloxacin:

Enterobacteriaceae: ≤0.5 µg/ml for susceptible, >1 µg/ml for resistant;
Pseudomonas spp. ≤0.5 µg/ml for susceptible, >1 µg/ml for resistant;
Acinetobacter spp. ≤1 µg/ml for susceptible, >1 µg/ml for resistant;
S. pneumonia ≤0.125 µg/ml for susceptible, >2 µg/ml for resistant;
Staphylococcus spp. ≤1 µg/ml for susceptible, >1 µg/ml for resistant;
H. influenza and M. catarrhalis ≤0.5 µg/ml for susceptible, >0.5 µg/ml for resistant;
Neisseria gonorrhoeae: ≤0.03 µg/ml for susceptible, >0.06 µg/ml for resistant;
N. meningitidis: ≤0.03 µg/ml for susceptible, >0.06 µg/ml for resistant;
Non-species related breakpoints are ≤1 µg/ml for susceptible, and >1 µg/ml for resistant organisms.

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. 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.

Commonly susceptible species
Gram-positive species
Bacillus anthracis
Gram-negative aerobe species
Citrobacter spp.
Enterobacter cloacae
Haemophilus influenzae
Moraxella spp.
Moraxella catarrhalis
Morganella spp.

Proteus spp.
Proteus mirabilis
Proteus vulgaris
Salmonella spp.
Serratia liquefaciens
Serratia marcescens
Shigella spp.
Shigella flexneri
Shigella sonnei
Species for which acquired resistance may be a problem
Gram-positive aerobes
Coagulase-negative *Staphylococcus*
Enterococcous faecalis
*MRSA**
Staphylococcus aureus
Staphylococcus aureus (methicillin susceptible)
Streptococcus spp.
Streptococcus agalactiae
Streptococcus pneumoniae
S. pneumoniae PEN-R
Streptococcus pyogenes
Gram-negative aerobes
Morganella morganii
Citrobacter freundii
Acinetobacter spp.
Acinetobacter baumannii

Campylobacter spp.
Campylobacter jejuni *Enterobacter* spp.
Enterobacter spp. Amp-C producing
Enterobacter aerogenes
Escherichia coli
E. coli ESBL producing
Klebsiella pneumoniae
Klebsiella oxytoca
Klebsiella pneumoniae ESBL producing
Neisseria gonorrhoeae
Pseudomonas aeruginosa
Inherently resistant organisms
Gram-positive aerobes
Enterococcus spp.
Enterococcus faecium
Staphylococcus epidermidis
Staphylococcus haemolyticus
Gram-negative aerobes
E. coli multi-resistant
Providencia spp.
Stenotrophomonas maltophilia
Other pathogens
Ureaplasma urealyticum

Anaerobes
Bacteroides fragilis

** MRSA is very likely to be resistant to ciprofloxacin and ciprofloxacin should not be used to treat presumed or known MRSA infections unless the organism is known to be susceptible.*

Abbreviations:

ESBL: Extended Spectrum Beta-lactamases

MRSA: Methicillin-resistant *Staphylococcus aureus*

Other information:

A study on Rhesus-monkeys that were exposed to anthrax by inhalation revealed that 8/9 animals survived the experiment when these animals were treated from 1 day after anthrax exposure with ciprofloxacin twice daily for a period of 30 days. The MIC of the *Bacillus anthrax* strain that was applied in this study was 0.08 µg/ml. Because the MIC_{90} for ciprofloxacin of 70 other *Bacillus anthrax* strains varied between 0.03-0.06 µg/ml, it seems likely that ciprofloxacin would also be effective in other strains than the one that was applied in this study. There are however no sufficient clinical data available to draw conclusion about the effectiveness of ciprofloxacin in the treatment of anthrax in humans. Physicians are recommended to follow current national and/or international consensus documents regarding the treatment of anthrax.

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 250 mg and 500 mg Cmax values are about 0.8-2.0mg/l and 1.5-2.9 mg/l respectively.

The absolute bioavailability is approximately 70 to 80%. Cmax 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 2-3l/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 clearnace lies between 3 and 5 ml/min/kg, and total clearance amounts to 8-10 ml/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 ciprofloxacin 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

Maize starch

Microcrystalline cellulose

Sodium starch glycollate

Colloidal Silicon dioxide

Methyl paraben

Propyl paraben

Purified talc

Magnesium stearate

White Pre-Mix

6.2. Incompatibilities

Not applicable

6.3. Shelf Life

2 years. Store in a cool dry place below $30^{o}C$

6.4. Special Precautions for Storage

No special precautions for storage.

For storage conditions of the medicinal product, see Section 6.3

6.5. Nature and Contents of Container

Ciprofloxacin 500 mg Film-Coated Tablets

10 film-coated tablets are packed in PVC/aluminum foil blisters and these blisters are packed in pouches along with an insert and sealed. 10 sealed pouches are packed in printed cartons.

6.6. Instructions for Use and Handling

No special requirements

7. Applicant / Supplier

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8. FDA Application number

AL0043/12

9. Date of Renewal of registration

28th May, 2019

10. Date of revision of the text

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