pharmaniaga®

Ciprofloxacin

Tablet 500mg

DESCRIPTION
White, oblong film-coated tablet with Pharmaniaga icon on one side and scored on the other.

COMPOSITION
Each film-coated tablet contains ciprofloxacin (as hydrochloride) 500 mg.

PHARMACODYNAMICS
Pharmacotherapeutic group: Fluoroquinolones,
ATC code: J01MA02

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

PK/PD 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:

In vitro susceptibility to ciprofloxacin

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

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms: *Bacillus anthracis*
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.
Aerobic Gram-negative micro-organisms: *Acinetobacter baumannii, Burkholderia cepacia, Campylobacter* spp., *Citrobacter freundii, Enterobacter aerogenes, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Neisseria gonorrhoeae, Proteus mirabilis, Proteus vulgaris, Providencia* spp., *Pseudomonas aeruginosa, Pseudomonas fluorescens, Serratia marcescens*
Anaerobic micro-organisms: *Peptostreptococcus* spp., *Propionibacterium acnes*

INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms: *Actinomyces, Enteroccus faecium, Listeria monocytogenes*
Aerobic Gram-negative micro-organisms: *Stenotrophomonas maltophilia*
Anaerobic micro-organisms: Excepted as listed above
Other micro-organisms: *Mycoplasma genitalium, Ureaplasma urealitycum*

PHARMACOKINETICS
Absorption and bioavailability: Following oral administration of single doses of 250 mg, 500 mg, and 750 mg, 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 volume: 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.

Metabolism: Low concentrations of four metabolites have been reported, which were identified as: Desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). 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 isoenzymes.

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. 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 hours. 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.

Available data shown 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%.

INDICATIONS
Consideration should be given to available official guidance on the appropriate use if antibacterial agents.

Uncomplicated and complicated infections caused by ciprofloxacin susceptible pathogens:
- *Infections of the respiratory tract: Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by *Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Moraxella catarrhalis, Legionella* and *Staphylococcus.*
- *Infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis), especially if these are caused by Gram-negative organisms including *Pseudomonas aeruginosa* or by staphylococci.
- Infections of the eyes
- *Infections of the kidneys and/or the efferent urinary tract
- Infections of the genital organs, including adnexitis, gonorrhea, prostatitis and excluding vaginal infections
- Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)
- Infections of the skin and soft tissue
- Infections of the bones and joints
- *Sepsis
- Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)
- Prophylaxis of invasive infections due to *Neisseria meningitidis.*

*Pharmaniaga Ciprofloxacin Tablet should be only used:
- When *Pseudomonas* is considered and the patient is allergic to antipseudomonal penicillins/ cephalosporin; or
- For resistant organisms with no other alternative antibiotics available.

Children and adolescents
Ciprofloxacin may be used in children for the second- and third-line treatment of complicated urinary tract infections and pyelonephritis due to *Escherichia coli* [age range applied in clinical studies: 1 – 17 years) and for the treatment of broncho-pulmonary infections of cystic fibrosis associated with *Pseudomonas* aeruginosa (age range applied in clinical studies: 5 – 17 years).

Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissues.

Inhalational anthrax (post-exposure) in adults and in children:
To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*.

CONTRAINDICATIONS
1. Hypersensitivity to ciprofloxacin or other quinolone or any of the excipients.
2. Concurrent administration of ciprofloxacin and tizanidine.

ADVERSE EFFECTS/UNDESIRABLE EFFECTS
The frequencies of ADRs reported with Pharmaniaga Ciprofloxacin Tablet 500mg are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

*Psychiatric disorders**
Uncommon: Psychomotor hyperactivity/agitation
Rare: Depression (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)
Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide)

Infections and Infestations
Uncommon: Mycotic superinfections
Rare: Antibiotic associated colitis (very rarely with possible fatal outcome)

Blood and Lymphatic System Disorders
Uncommon: Eosinophilia
Rare: Leukopenia, anemia, neutropenia, leukocytosis, thrombocytopenia, thrombocytaemia
Very rare: Haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening)

Immune System Disorders
Rare: Allergic reaction, allergic oedema/angioedema
Very rare: Anaphylactic reaction, anaphylactic shock (life-threatening), Serum sickness-like reaction.

Metabolism and Nutrition Disorders
Uncommon: Decreased appetite and food intake
Rare: Hyperglycemia, hypoglycemia

*Nervous System Disorders**
Uncommon: Headache, dizziness, sleep disorders, taste disorders.
Rare: Par- and dysaesthesia, hypoaesthesia, tremor, seizures (including status epilepticus), vertigo
Very rare: Migraine, disturbed coordination, smell disorders, hyperesthesia, intracranial hypertension (pseudotumor cerebri)
Not known: Peripheral neuropathy and polyneuropathy

*Eye Disorders**
Rare: Visual disturbances
Very rare: Visual color distortions

*Ear and Labyrinth Disorders**
Rare: Tinnitus, hearing loss
Very rare: Hearing impaired

Cardiac Disorders
Rare: Tachycardia
Not known: QT prolongation, ventricular arrhythmia, torsades de pointes (reported predominantly in patients with risk factors for QT prolongation)

Vascular Disorders
Rare: Vasodilatation, hypotension, syncope
Very rare: Vasculitis

Respiratory, Thoracic and Mediastinal Disorders
Rare: Dyspnea (including asthmatic condition)

Gastrointestinal Disorders
Common: Nausea, diarrhea
Uncommon: Vomiting, gastrointestinal and abdominal pain, dyspepsia, flatulence
Very rare: Pancreatitis

Hepatobiliary Disorders
Uncommon: Increase in transaminases, increased bilirubin
Rare: Hepatic impairment, jaundice, hepatitis (non-infective)
Very rare: Liver necrosis (very rarely progressing to life-threatening hepatic failure)

Skin and Subcutaneous Tissue Disorders
Uncommon: Rash, pruritus, urticaria
Rare: Photosensitivity reactions, blistering
Very rare: Petechiae, erythema multiforme, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), Toxic epidermal necrolysis (potentially life-threatening)
Not known: Acute generalised exanthematous pustulosis

*Musculoskeletal, Connective Tissue and Bone Disorders**
Uncommon: Arthralgia
Rare: Myalgia, arthritis, increased muscle tone and cramping
Very rare: Muscular weakness, tendinitis, tendon rupture (predominantly Achilles tendon), exacerbation of symptoms of Myasthenia Gravis

Renal and Urinary Disorders
Uncommon: Renal impairment
Rare: Renal failure, hematuria, crystalluria, tubulointerstitial nephritis

*General Disorders and Administration Site Conditions**
Uncommon: Unspecified pain, feeling unwell, fever
Rare: Oedema, sweating (hyperhidrosis)
Very rare: Gait disturbance

Investigations
Uncommon: Increased in blood alkaline phosphatase
Rare: Abnormal prothrombin level, increased amylase
Not known: International normalized ratio increased (in patients treated with Vitamin K antagonists)

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiples, system organ classes and senses (including reactions such as tendinitis, tendon rupture, arthralgia, pain in extremities, gait disturbance, neuropathies associated with paraesthesia, depression, fatigue, memory impairment, sleep disorders and impairment of hearing, vision, taste and smell) have been reported in association with the use of fluoroquinolones in some cases irrespective of pre-existing risk factors.

In isolated instances, some serious adverse drug reactions may be long-lasting (>30 days) and disabling such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbances of sense.

The following undesirable effects have a higher frequency category in the subgroups of patients receiving sequential (intravenous to oral) treatment:

Common	Vomiting, transient increase in transaminases, rash
Uncommon	Thrombocytopenia, thrombocytaemia, confusion and disorientation, hallucinations, par- and dysaesthesia, seizures, vertigo, visual disturbances, hearing loss, tachycardia, vasodilatation, hypotension, transient hepatic impairment, jaundice, renal failure, oedema
Rare	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impaired, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

Paediatric patients
The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to adults. In children, arthropathy is reported to occur commonly.

WARNINGS AND PRECAUTIONS
The use of Pharmaniaga Ciprofloxacin Tablet should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products. Treatment of these patients with Pharmaniaga Ciprofloxacin Tablet should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

Psychiatric reactions: Psychiatric reactions may occur even after the first administration of fluoroquinolones, including ciprofloxacin. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behavior, such as attempted or completed suicide. In the event that the patient develops these reactions, Pharmaniaga Ciprofloxacin Tablet should be discontinued and appropriate measures instituted. Caution is recommended if Pharmaniaga Ciprofloxacin Tablet is to be used in psychotic patients or in patients with a history of psychiatric disease.

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

Tendinitis and tendon rupture: 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 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 (above 60 years of age), 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. immobilization). Corticosteroids should not be used if signs of tendinopathy occur.

Peripheral neuropathy: Cases of sensory or sensorimotor polyneuropathy resulting in paraeathesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Pharmaniaga Ciprofloxacin Tablet should be advised to inform their doctor and pharmacist 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.

Aortic aneurysm and dissection: Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis). In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Cytochrome P450: Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicinal products are administered concomitantly which are metabolized via the same enzymatic pathway (e.g. theophylline, methylxantines, caffeine, duloxetine, ropinirole, clozapine, olanzapine, agomelatine). Increased plasma concentrations associated with drug-specific undesirable effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin.

Gastrointestinal system: In the event of severe and persistent diarrhoea during or after treatment a doctor must be consulted since this symptom can hide a serious intestinal disease (life threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment. In such cases, Pharmaniaga Ciprofloxacin Tablet must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250 mg/day). Medicinal products that inhibit peristalsis are contraindicated in this situation.

Hypersensitivity: In some instances, the hypersensitivity and allergic reactions already occurred after the first administration and the doctor should be informed immediately. Anaphylactic reactions in very rare instances can progress to a life threatening shock, in some instances after the first administration. In these cases Pharmaniaga Ciprofloxacin Tablet has to be discontinued and medical treatment is required.

Exacerbation of myasthenia gravis: Pharmaniaga Ciprofloxacin Tablet should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated. Fluoroquinolones have neuromuscular blocking activity and may exacerbate muscle weakness in person with myasthenia gravis. Post marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluoroquinolones use in persons with myasthenia gravis. Avoid fluoroquinolones in patients with known history of myasthenia gravis.

Skin and appendages: Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking Pharmaniaga Ciprofloxacin Tablet should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitization occurs.

Severe infections and/or infections due to Gram-positive or anaerobic bacteria: For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, Pharmaniaga Ciprofloxacin Tablet should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections: Pharmaniaga Ciprofloxacin Tablet is not recommended for treatment of pneumococcal infections due to inadequate efficacy against *Streptococcus pneumoniae*.

Genital tract infections: Genital tract infections may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae isolates*. In genital tract infections thought or known to be due to *Neisseria gonorrhoeae*, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

Cardiac disorders: Ciprofloxacin is associated with cases of QT prolongation. As women tend to have a longer baseline QTc interval compared with men they may be more sensitive to QTc-prolonging medications. Elderly patients may also be more susceptible to drug-associated effects on the QT interval. Precaution should be taken when using ciprofloxacin with concomitant drugs that can result in prolongation with the QT interval (e.g. class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) or in patients with risk factors for QT prolongation or torsade de pointes (e.g.congenital long QT syndrome, uncorrected electrolyte imbalance such as hypokalemia or hypomagnesemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia).

Children and adolescents: Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. The analysis of available safety data from ciprofloxacin use in patients less than 18 years of age, the majority of whom had cystic fibrosis, did not disclose any evidence of drug-related cartilage or articular damage. The use of ciprofloxacin for indications other than the treatment of broncho-pulmonary infections of cystic fibrosis caused by *Pseudomonas aeruginosa* infection (children aged 5 – 17 years), complicated urinary tract infections and pyelonephritis due to *Escherichia coli* (children aged 1 – 17 years), and for the use in inhalational anthrax (post-exposure) was not studied. For other indications clinical experience is limited.

Interaction with tests: Ciprofloxacin in vitro potency may interfere with the *Mycobacterium tuberculosis*. culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking Pharmaniaga Ciprofloxacin Tablet.

Hepatobiliary system: Cases of hepatic necrosis and life-threatening hepatic failure have been reported with ciprofloxacin. 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. There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage, who are treated with Pharmaniaga Ciprofloxacin Tablet.

Dysglycaemia: As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Pharmaniaga Ciprofloxacin Tablet. In Pharmaniaga Ciprofloxacin Tablet-treated patients, dysglycemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended.

Seizures: Pharmaniaga Ciprofloxacin Tablet like other fluoroquinolones, is known to trigger seizures or lower the seizure threshold. In epileptics and patients who have suffered from previous central nervous system (CNS) disorders (e.g. lowered convulsion threshold, previous history of convulsion, reduced cerebral blood flow, altered brain structure, or stroke), ciprofloxacin should only be used where the benefits of treatment exceed the risks, since these patients are endangered because of possible undesirable CNS effects. Cases of status epilepticus have been reported. If seizures occur, Pharmaniaga Ciprofloxacin Tablet should be discontinued.

PREGNANCY AND LACTATION

Pregnancy: The data, that are available from the use of ciprofloxacin in pregnant women, indicate neither malformative nor feto/neonatal toxicity. Animal studies do not indicate reproductive toxicity. Based on animal studies, it cannot be excluded that the drug could cause damage to articular cartilage in the immature fetal organism, therefore, the use of Pharmaniaga Ciprofloxacin Tablet is not recommended during pregnancy. Animal studies have not shown any evidence of teratogenic effects (malformations).

Lactation: Ciprofloxacin is excreted in breast milk. Due to potential risk of articular damage, Pharmaniaga Ciprofloxacin Tablet is not recommended during breast-feeding.

INTERACTION WITH OTHER MEDICAMENTS

Chelation Complex Formation: The simultaneous administration of Pharmaniaga Ciprofloxacin Tablet and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of Pharmaniaga Ciprofloxacin Tablet. Consequently, ciprofloxacin should be administered either 1-2 hours before or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Food and Dairy Products: The concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) and Pharmaniaga Ciprofloxacin Tablet should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

Omeprazole: Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Theophylline: Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in the serum theophylline concentration. This can lead to theophylline-induced side effects; in very rare cases these side effects can be life threatening or fatal. If concurrent use of the two products is unavoidable, serum theophylline concentration should be checked and theophylline dose appropriately reduced.

NSAID: Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Cyclosporin: A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin were administered simultaneously. It is necessary to control the serum creatinine concentrations in these patients frequently (twice a week).

Probenecid: Probenecid interferes with renal secretion of Pharmaniaga Ciprofloxacin Tablet. Co-administration of probenecid containing medicinal products and ciprofloxacin increases ciprofloxacin serum concentrations.

Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of Pharmaniaga Ciprofloxacin Tablet potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

Metoclopramide: Metoclopramide accelerates the absorption of Pharmaniaga Ciprofloxacin Tablet resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Tizanidine: There was an increase in tizanidine serum concentrations when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect. Tizanidine containing medicinal products must not be administered together with Pharmaniaga Ciprofloxacin Tablet.

Duloxetine: 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.

Ropinirole: Concomitant use of ropinirole with ciprofloxacin, a medium inhibitor of the CYP450 1A2 isozyme, resulted in increases in the C_{max} and AUC of ropinirole. Monitoring ropinirole-related undesirable effects dose adjustment as appropriate is recommended during and shortly after coadministration with Pharmaniaga Ciprofloxacin Tablet.

Lidocaine: Concomitant use of lidocaine with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine. 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 ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with Pharmaniaga Ciprofloxacin Tablet are advised.

Drugs known to prolong QT interval: Pharmaniaga Ciprofloxacin Tablet should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

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

Vitamin K antagonists: Simultaneous administration of Pharmaniaga Ciprofloxacin Tablet with a vitamin K antagonist may augment its anticoagulant 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 Pharmaniaga Ciprofloxacin Tablet with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

Sildenafil: C_{max} and AUC of sildenafil were increased. Caution should be used prescribing Pharmaniaga Ciprofloxacin Tablet concomitantly with sildenafil taking into consideration the risks and the benefits.

Phenytoin: Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving Pharmaniaga Ciprofloxacin Tablet and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related undesirable effects when Pharmaniaga Ciprofloxacin Tablet is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of Pharmaniaga Ciprofloxacin Tablet with phenytoin.

Agomelatine: 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.

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

DOSAGE AND ADMINISTRATION

Dosage regimen

Unless otherwise prescribed, the following daily dose are recommended:

Adult

Recommended daily doses of Pharmaniaga Ciprofloxacin Tablet in adult;

Indications	Daily dose of ciprofloxacin in mg for Pharmaniaga Ciprofloxacin Tablet
Infections of the respiratory tract I (according to severity and organism)	2 x 500mg to 2 x 750mg
Urinary tract infections 1) Acute, uncomplicated 2) Cystitis in women (before menopause) 3) Complicated	 1) 2 x 250mg to 2 x 500mg 2) Single dose 500mg 3) 2 x 500mg to 2 x 750mg
Genital infections 1) Uncomplicated gonorrhea (including extragenital sites of infection) 2) Adnexitis, prostatitis, epididymo-orchitis	 1) 1 x 500mg 2) 2 x 500mg to 2 x 750mg
Diarrhea	2 x 500mg
Other infections (see indications)	2 x 500mg
Particularly severe, life-threatening infections,i.e. - Recurrent infections in cystic fibrosis - Bone and joint infections - Septicemia - Peritonitis In particular when *Pseudomonas*, *Staphylococcus* or *Streptococcus* is present	2 x 750mg
Inhalational anthrax (post exposure)	2 x 500mg
Prophylaxis of invasive infections due to *Neisseria meningitides*	1 x 500mg as a single dose

Children and adolescents

Recommended daily doses of Pharmaniaga Ciprofloxacin Tablet in children and adolescent;

Indication	Daily dose of ciprofloxacin in mg for Pharmaniaga Ciprofloxacin Tablet
Infections in cystic fibrosis	2 x 20mg/kg body weight (maximum of 750mg per dose)
Complicated urinary tract infection and pyelonephritis	2 x 10mg/kg body weight to 2 x 20mg/kg body weight (maximum of 750mg per dose)
Inhalation anthrax (post-exposure)	2 x 15mg/kg body weight (maximum of 500mg per dose)

Additional information on special patient population

1. *Geriatric patients (> 65 years)*
   Elderly patients should receive a dose as low as possible depending on the severity of their illness and the creatinine clearance.
2. *Patients with renal and hepatic impairment*
   Adults
   Recommended doses for patients with renal impairment

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [mg/100mL]	Total daily oral dose of ciprofloxacin
30 to 60	1.4 to 1.9	maximum 1000mg
below 30	≥ 2.0	maximum 500mg

Patients with renal impairment on hemodialysis

- For patients with creatinine clearance between 30 and 60 mL/min/1.73m² (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 mL, the maximum daily oral dose of ciprofloxacin should be 1000 mg.
- For patients with creatinine clearance less than 30 mL/min/1.73m² (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 mL, the maximum daily oral dose of ciprofloxacin should be 500 mg on dialysis days after dialysis..

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD)

- The maximum daily oral dose of ciprofloxacin should be (1 x 500mg ciprofloxacin tablet).

Patients with renal impairment

- In patients with impaired hepatic function no dose adjustment is required.

Patients with renal and hepatic impairment

- For patients with creatinine clearance between 30 and 60mL/min/1.73m² (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9mg/100mL, the maximum daily oral dose of ciprofloxacin should be 1000mg.
- For patients with creatinine clearance less than 30mL/min/1.73m² (severe renal impairment) or serum creatinine concentration equal or higher than 2.0mg/100mL, the maximum daily oral dose of ciprofloxacin should be 500mg.

Children and adolescent

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

Missed dose

If a dose is missed, it should be taken as anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Method of Administration

For oral use.

Ciprofloxacin tablets are to be swallowed whole with a small amount of fluid and can be taken independently of mealtimes.

If they are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, ciprofloxacin tablets should not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice). If the patient is unable to take ciprofloxacin tablets because of the severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration, the treatment can be continued orally.

Duration of Treatment

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms.

Mean duration of treatment:

Adults

- 1 day for acute uncomplicated gonorrhea and cystitis
- up to 7 days for infections of the kidneys, urinary tract and abdominal cavity
- over the entire period of the neutropenic phase in patients with weakened body defenses
- a maximum of 2 months in osteomyelitis
- 7 – 14 days in all other infections

In *streptococcal* infections, the treatment must last at least ten days because of the risk of late complications.

Infections caused by *Chlamydia* spp. should also be treated for a minimum of ten days.

Children and adolescents

- Cystic Fibrosis

For broncho-pulmonary infections of cystic fibrosis associated with *Pseudomonas aeruginosa* infection in pediatric patients (aged 5 – 17 years), the duration of treatment is 10 – 14 days.

- Complicated Urinary Tract Infections and Pyelonephritis

For complicated urinary tract infections or pyelonephritis due to *Escherichia coli*, the duration of treatment is 10 – 21 days.

- Inhalational Anthrax (Post-exposure) in Adults and Children

60 days from the confirmation of *Bacillus anthracis* exposure

EFFECTS ON ABILITY TO DRIVE OR USE MACHINE

Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions (see 'Adverse Effects/Undesirable Effects'). This applies particularly in combination with alcohol.

OVERDOSAGE

Reversible renal toxicity has been reported in some cases. Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required to prevent crytalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses.

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

STORAGE CONDITIONS

Store below 30°C.
Protect from light.

SHELF LIFE

Product should not be used beyond the expiry date imprinted on the packaging.

PRESENTATION

In blisters of 10, 20, 30 and 100 tablets.

Date of revision: 08th December 2025

PRODUCT REGISTRATION HOLDER/ MANUFACTURER:
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