CIPROFLOXACIN HCl

PYCIP

Antibacterial

FORMULATION

Active Ingredient: Each film-coated tablet contains Ciprofloxacin hydrochloride equivalent to Ciprofloxacin 500 mg.

Other Ingredients: Pregelatinized starch, Maize starch, Magnesium stearate, Sodium starch glycolate, Opadry white, Titanium dioxide.

PHARMACODYNAMICS

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive microorganisms. The bactericidal action of Ciprofloxacin results from inhibition of the enzymes topoisomerase II (DNA gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair, and recombination. The mechanism of action of fluoroquinolones, including Ciprofloxacin, is different from that of penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines; therefore, microorganisms resistant to these classes of drugs may be susceptible to ciprofloxacin and other quinolones. Ciprofloxacin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical infections as following:

Aerobic Gram-positive microorganisms

Enterococcus faecalis (many strains are only moderately susceptible), *Staphylococcus aureus* (methicillin-susceptible strains only), *Staphylococcus epidermidis* (methicillin-susceptible strains only), *Staphylococcus saprophyticus, Streptococcus pneumoniae* (penicillin-susceptible strains only), *Streptococcus pyogenes.*

Aerobic Gram-negative microorganisms

Campylobacter jejuni, Proteus mirabilis, Citrobacter diversus, Proteus vulgaris, Citrobacter freundii, Providencia rettgeri, Enterobacter cloacae, Providencia stuartii, Escherichia coli, Pseudomonas aeruginosa, Haemophilus influenzae, Salmonella typhi, Haemophilus parainfluenzae, Serratia marcescens, Klebsiella pneumoniae, Shigella boydii, Moraxella catarrhalis, Shigella dysenteriae, Morganella morganii, Shigella flexneri, Neisseria gonorrhoeae, Shigella sonnei.

PHARMACOKINETICS

- Ciprofloxacin given as an oral tablet is rapidly and well absorbed from the gastrointestinal tract after oral administration. The absolute bioavailability is approximately 70% with no substantial loss by first pass metabolism.

- The binding of Ciprofloxacin to serum proteins is 20 to 40%. After oral administration, Ciprofloxacin is widely distributed throughout the body. Tissue concentrations often exceed serum concentrations in both men and women, particularly in genital tissue including the prostate. The drug diffuses into the cerebrospinal fluid (CSF); however, CSF concentrations are generally less than 10% of peak serum concentrations. Low levels of the drug have been detected in the aqueous and vitreous humors of the eye.

- Four metabolites have been identified in human urine which together account for approximately 15% of an oral dose. The metabolites have antimicrobial activity, but are less active than unchanged Ciprofloxacin. Ciprofloxacin is an inhibitor of human cytochrome P450 1A2 (CYP1A2) mediated metabolism.

- The serum elimination half-life in subjects with normal renal function is approximately 4 hours. Approximately 40 to 50% of an orally administered dose is excreted in the urine as unchanged drug. The urinary excretion of Ciprofloxacin is virtually complete within 24 hours after dosing. Although bile concentrations of Ciprofloxacin are several fold higher than serum concentrations after oral dosing, only a small amount of the dose administered is recovered from the bile as unchanged drug. Approximately 20 to 35% of an oral dose is recovered from the feces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

INDICATIONS

Acute Sinusitis caused by *Haemophilus influenzae, penicillin-susceptible Streptococcus pneumoniae*, or *Moraxella catarrhalis.*

Lower Respiratory Tract Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenzae, Haemophilus parainfluenzae,* or *penicillin-susceptible Streptococcus pneumoniae.* Also, *Moraxella catarrhalis* for the treatment of acute exacerbations of chronic bronchitis.

NOTE: Although effective in clinical trials, Ciprofloxacin is not a drug of first choice in the treatment of presumed or confirmed pneumonia secondary to *Streptococcus pneumoniae.*

Urinary Tract Infections caused by *Escherichia coli, Klebsiella pneumonia, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, methicillin-susceptible Staphylococcus epidermidis, Staphylococcus saprophyticus,* or *Enterococcus faecalis.*

Acute Uncomplicated Cystitis in females caused by *Escherichia coli* or *Staphylococcus saprophyticus.*

Chronic Bacterial Prostatitis caused by *Escherichia coli* or *Proteus mirabilis.*

Complicated Intra-Abdominal Infections (used in combination with metronidazole) caused by *Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Klebsiella pneumoniae,* or *Bacteroides fragilis.*

Skin and Skin Structure Infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus aureus (methicillin-susceptible), Staphylococcus epidermidis, or Streptococcus pyogenes.*

Bone and Joint Infections caused by *Enterobacter cloacae, Serratia marcescens,* or *Pseudomonas aeruginosa.*

Infectious Diarrhea caused by *Escherichia coli* (enterotoxigenic strains), *Campylobacter jejuni, Shigella boydii, Shigella dysenteriae, Shigella flexneri* or *Shigella sonnei* when antibacterial therapy is indicated.

Typhoid Fever (Enteric Fever) caused by *Salmonella typhi.*

NOTE: The efficacy of Ciprofloxacin in the eradication of the chronic typhoid carrier state has not been demonstrated.

Uncomplicated cervical and urethral gonorrhea due to *Neisseria gonorrhoeae.*

CONTRAINDICATIONS

Ciprofloxacin tablets are contraindicated in persons with a history of hypersensitivity to Ciprofloxacin, any member of the quinolone class of antimicrobial agents, or any of the product components.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fluoroquinolones, including Ciprofloxacin, are associated with an increased risk of tendinitis and tendon rupture in all ages. This adverse reaction most frequently involves the Achilles tendon, and rupture of the Achilles tendon may require surgical repair. Tendinitis and tendon rupture in the rotator cuff (the shoulder), the hand, the biceps, the thumb, and other tendon sites have also been reported. The risk of developing fluoroquinolone-associated tendinitis and tendon rupture is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart or lung transplants. Factors, in addition to age and corticosteroid use, that may independently increase the risk of tendon rupture include strenuous physical activity, renal failure, and previous tendon disorders such as rheumatoid arthritis. Tendinitis and tendon rupture have also occurred in patients taking fluoroquinolones who do not have the above risk factors. Tendon rupture can occur during or after completion of therapy; cases occurring up to several months after completion of therapy have been reported. Ciprofloxacin should be discontinued if the patient experiences pain, swelling, inflammation or rupture of a tendon. Patients should be advised to rest at the first sign of tendinitis or tendon rupture, and to contact their healthcare provider regarding changing to a non-quinolone antimicrobial drug.

PRECAUTIONS

General

Crystals of Ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals, which is usually alkaline. Crystalluria related to Ciprofloxacin has been reported only rarely in humans because human urine is usually acidic. Alkalinity of the urine should be avoided in patients receiving Ciprofloxacin. Patients should be well hydrated to prevent the formation of highly concentrated urine.

Central Nervous System

Quinolones, including Ciprofloxacin, may also cause central nervous system (CNS) events, including: nervousness, agitation, insomnia, anxiety, nightmares or paranoia.

Renal Impairment

Alteration of the dosage regimen is necessary for patients with impairment of renal function.

Photosensitivity/Phototoxicity

Moderate to severe photosensitivity/phototoxicity reactions, the latter of which may manifest as exaggerated sunburn reactions (e.g., burning, erythema, exudation, vesicles, blistering, edema) involving areas exposed to light (typically the face,"V" area of the neck, extensor surfaces of the forearms, dorsa of the hands), can be associated with the use of quinolones after sun or UV light exposure. Therefore, excessive exposure to these sources of light should be avoided. Drug therapy should be discontinued if phototoxicity occurs.

As with any potent drug, periodic assessment of organ system functions, including renal, hepatic, and hematopoietic function, is advisable during prolonged therapy.

Prescribing Ciprofloxacin in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

INTERACTION WITH OTHER DRUGS

As with some other quinolones, concurrent administration of Ciprofloxacin with theophylline

may lead to elevated serum concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, serum levels of theophylline should be monitored and dosage adjustments made as appropriate.

Some quinolones, including Ciprofloxacin, have also been shown to interfere with the metabolism of caffeine. This may lead to reduced clearance of caffeine and a prolongation of its serum half-life.

Concurrent administration of a quinolone, including Ciprofloxacin, with multivalent cation-containing products such as magnesium/aluminum antacids, sucralfate, didanosine chewable/buffered tablets or pediatric powder, other highly buffered drugs, or products containing calcium, iron, or zinc may substantially decrease its absorption, resulting in serum and urine levels considerably lower than desired.

Histamine H2-receptor antagonists appear to have no significant effect on the bioavailability of Ciprofloxacin.

Altered serum levels of phenytoin (increased and decreased) have been reported in patients receiving concomitant Ciprofloxacin.

The concomitant administration of Ciprofloxacin with the sulfonylurea glyburide has, on rare occasions, resulted in severe hypoglycemia.

Some quinolones, including Ciprofloxacin, have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.

Quinolones, including Ciprofloxacin, have been reported to enhance the effects of the oral anticoagulant warfarin or its derivatives. When these products are administered concomitantly, prothrombin time or other suitable coagulation tests should be closely monitored.

Probenecid interferes with renal tubular secretion of Ciprofloxacin and produces an increase in the level of Ciprofloxacin in the serum. This should be considered if patients are receiving both drugs concomitantly.

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.

Metoclopramide significantly accelerates the absorption of oral Ciprofloxacin resulting in shorter time to reach maximum plasma concentrations. No significant effect was observed on the bioavailability of Ciprofloxacin.

Non-steroidal anti-inflammatory drugs (but not acetyl salicylic acid) in combination of very high doses of quinolones have been shown to provoke convulsions in pre-clinical studies.

DOSAGE AND ADMINISTRATION

Ciprofloxacin should be administered orally to adults as described in the Dosage Guidelines table.

The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, the integrity of the patient's hostdefense mechanisms, and the status of renal function and hepatic function.

The duration of treatment depends upon the severity of infection. The usual duration is 7 to 14 days; however, for severe and complicated infections more prolonged therapy may be required. Ciprofloxacin should be administered at least 2 hours before or 6 hours after magnesium/aluminum antacids, or sucralfate, didanosine chewable/buffered tablets or pediatric powder for oral solution, other highly buffered drugs, or other products containing calcium, iron or zinc.

ADULT DOSAGE GUIDELINES

Infection	Severity	Dose	Frequency	Usual Durations
Urinary Tract	Acute Uncomplicated	250 mg	Every 12 hrs	3 days
	Mild/Moderate	250 mg	Every 12 hrs	7 to 14 days
	Severe/Complicated	500 mg	Every 12 hrs	7 to 14 days
Chronic Bacterial Prostatitis	Mild/Moderate	500 mg	Every 12 hrs	28 days
Lower Respiratory Tract	Mild/Moderate	500 mg	Every 12 hrs	7 to 14 days
	Severe/Complicated	500 mg	Every 12 hrs	7 to 14 days
Acute Sinusitis	Mild/Moderate	500 mg	Every 12 hrs	10 days
Skin and Skin Structure	Mild/Moderate	500 mg	Every 12 hrs	7 to 14 days
	Severe/Complicated	750 mg	Every 12 hrs	7 to 14 days
Bone and Joint	Mild/Moderate	500 mg	Every 12 hrs	= 4 to 6 weeks
	Severe/Complicated	750 mg	Every 12 hrs	= 4 to 6 weeks
Intra-Abdominal †*	Complicated	500 mg	Every 12 hrs	7 to 14 days
Infectious Diarrhea	Mild/Moderate/Severe	500 mg	Every 12 hrs	5 to 7 days
Typhoid Fever	Mild/Moderate	500 mg	Every 12 hrs	10 days
Urethral and Cervical	Uncomplicated	250 mg	single dose	single dose
Gonococcal Infections Inhalational anthrax		500 mg	Every 12 hrs	60 days

* Generally Ciprofloxacin should be continued for at least 2 days after the signs and symptoms of infection have disappeared, except for inhalational anthrax (post-exposure).

† Used in conjunction with metronidazole.

Adults with Impaired Renal Function:

Ciprofloxacin is eliminated primarily by renal excretion; however, the drug is also metabolized and partially cleared through the biliary system of the liver and through the intestine. These alternative pathways of drug elimination appear to compensate for the reduced renal excretion in patients with renal impairment. Nonetheless, some modification of dosage is recommended, particularly for patients with severe renal dysfunction. The following table provides dosage guidelines for use in patients with renal impairment:

RECOMMENDED STARTING AND MAINTENANCE DOSES FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

Creatinine Clearance (mL/min)	Dose
> 50	See Usual Dosage.
30 – 50	250 – 500 mg every 12 hrs
5 – 29	250 – 500 mg every 18 hrs
Patients on hemodialysis or Peritoneal dialysis	250 – 500 mg every 24 hrs (after dialysis)

ADVERSE EFFECTS

BODY AS A WHOLE: headache, abdominal pain/discomfort, foot pain, pain in extremities, injection site reaction (intravenous Ciprofloxacin).

CARDIOVASCULAR: palpitation, atrial flutter, ventricular ectopy, syncope, hypertension, angina pectoris, myocardial infarction, cardiopulmonary arrest, cerebral thrombosis, phlebitis, tachycardia, migraine, hypotension.

CENTRAL NERVOUS SYSTEM: restlessness, dizziness, lightheadedness, insomnia, nightmares, hallucinations, manic reaction, irritability, tremor, ataxia, convulsive seizures, lethargy, drowsiness, weakness, malaise, anorexia, phobia, depersonalization, depression, paresthesia, abnormal gait, grand mal convulsion.

GASTROINTESTINAL: painful oral mucosa, oral candidiasis, dysphagia, intestinal perforation, gastrointestinal bleeding, cholestatic jaundice, hepatitis.

HEMIC/LYMPHATIC: lymphadenopathy, petechia.

METABOLIC/NUTRITIONAL: amylase increase, lipase increase.

MUSCULOSKELETAL: arthralgia or back pain, joint stiffness, achiness, neck or chest pain, flare up of gout.

RENAL/UROGENITAL: nephritis, interstitial nephritis, renal failure, polyuria, urinary retention, urethral bleeding, vaginitis, acidosis, breast pain.

RESPIRATORY: dyspnea, epistaxis, laryngeal or pulmonary edema, hiccough, hemoptysis, bronchospasm, pulmonary embolism.

SKIN/HYPERSENSITIVITY: allergic reaction, pruritus, urticaria, photosensitivity/phototoxicity reaction, flushing, fever, chills, angioedema, edema of the face, neck, lips, conjunctivae or hands, cutaneous candidiasis, hyperpigmentation, erythema nodosum, sweating.

SPECIAL SENSES: blurred vision, disturbed vision (change in color perception, overbrightness of lights), decreased visual acuity, diplopia, eye pain, tinnitus, hearing loss, bad taste, chromatopsia.

In several instances nausea, vomiting, tremor, irritability, or palpitation were judged by investigators to be related to elevated serum levels of theophylline possibly as a result of drug interaction with Ciprofloxacin. In randomized, double-blind controlled clinical trials comparing Ciprofloxacin tablets (500 mg twice daily) to cefuroxime axetil (250 mg - 500 mg twice daily) and to clarithromycin (500 mg twice daily) in patients with respiratory tract infections, Ciprofloxacin demonstrated a CNS adverse event profile comparable to the control drugs.

SHELF LIFE AND STORAGE INSTRUCTIONS

The expiry date of this medicinal product is printed on the box and blister foil.

Store at temperatures not exceeding 30°C.

Protect from light.

Do not use this medicinal product after the expiry date.

KEEP OUT OF REACH OF CHILDREN.

CAREFULLY READ THE PACKAGE INSERT BEFORE USE.

AVAILABILITY

Ciprofloxacin 500 mg film-coated tablet appears as white film-coated caplet, with a fracture line on one side and flat on the other side. Blister packed in white opaque PVC/aluminum blister and packed in card box (10 tablets x 10 blisters packs).

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

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