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For the use of Medical Practitioner or a Hospital or a Laboratory only

Ificipro* 250/500

Ciprofloxacin Tablets USP 250 mg/500 mg

Composition:
Each film coated tablet contains:
Ciprofloxacin Hydrochloride USP eq. to Ciprofloxacin 250mg / 500 mg.

Description:
Ificipro 250mg tablets (Ciprofloxacin Tablets 250mg):
White to yellowish white, round biconvex, film coated tablets.

Ificipro 500mg tablets (Ciprofloxacin Tablets 500mg):
White to yellowish white, capsule shaped film coated tablets with break line on one side and other side plain.

Pharmacodynamics:
Ciprofloxacin is from the quinolone group; these substances are also known as gyrase inhibitors.

Microbiology:
Gram-Negative Organisms
Enterobacteriaceae including *E.coli, Salmonella* species, *Klebsiella* species, *Shigella, Proteus mirabilis, Proteus vulgaris, K. oxytoca, Yersinia enterocolitica, Enterobacter, Citrobacter, Morganella morganii, Pseudomonas aeruginosa, Hemophilus Influenza, Acinetobacter, Campylobacter, Brucella melitensis, Pasteurella multocida, Eikenella corrodenus, Flavobacterium, Moraxella, Gardenerella Vaginalis, Legionells* species, *Vibrio cholerae* and *Vibrio parahernolyticus, Neisseria meningitidis* and *Neisseria gonorrhea* including b-lactomase producing strains.

Gram-Positive Organisms
Staphylococcus aureus including *b-lactamase* producing and *methicillin-resistant strains, streptococcus pneumoniae group A 8-hemolytic streptococci,* group B *streptococci* and other *streptococci, Enterococci including Enterococcus faecalis, Corynebacterium* and *Listeria monocytogenes.*

Other microorganisms
Anaerobic bacteria including *actinomyces, Bifidobacterium, Peptococcus, Clostridium perfringens, Eubacterium, Propioribactirium acres*, *Veiiionella* and some strains of *Baderoides, Chlamydia, Mycoplasma and Mycobacterium*. Ificipro is effective against organisms resistant to nalidixic acid. Since cross-resistance is unlikely, Ificipro may be used to treat infections caused by organism resistant to other class of antibacterial such as aminoglycosides, penicillin, sulfonamides, tetracyclines and cephalosporins.

Pharmacokinetics:
Absorption of oral doses of ciprofloxacin tablet formulation occurs rapidly, mainly from the small intestine, the half-life of absorption being 2-15 minutes. Plasma levels are dose-related and peak 0.5-2.0 hours after dosing. The AUC also increases dose proportionately after administration of both single and repeated oral (tablet) and intravenous doses. The absolute bioavailability is reported to be 52-83% and ciprofloxacin is subject to only slight first pass metabolism. The oral bioavailability is approximately 70-80%.

The intake of food at the same time as administration of oral ciprofloxacin has a marginal but clinically not relevant effect on the pharmacokinetic parameters Cmax and AUC. No specific recommendations are necessary with regard to time of administration of oral ciprofloxacin relative to food intake.

Distribution of ciprofloxacin within tissues is wide and the volume of distribution high, though slightly lower in the elderly. Protein binding is low (between 19-40%).

Only 10-20% of a single oral or intravenous dose is eliminated as metabolites (which exhibit lower activity than the parent drug). Four different antimicrobially active metabolites have been reported, desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxaciprofloxacin (M3) and formylciprofloxacin (M4). M2 and M3 account for one third each of metabolised substance and M1 is found in small amounts (1.3-2.6% of the dose). M4 has been found in very small quantities (<0.1% of the dose). M1-M3 have antimicrobial activity comparable to nalidixic acid and M4 found in the smallest quantity has antimicrobial activity similar to that of norfloxacin. Elimination of ciprofloxacin and its metabolites occurs rapidly, primarily by the kidney. After single oral and intravenous doses of ciprofloxacin, 55% and 75% respectively are eliminated by the kidney and 39% and 14% in the faeces within 5 days. Renal elimination takes place mainly during the first 12 hours after dosing and renal clearance levels suggest that active secretion by the renal tubules occurs in addition to normal glomerular filtration. Renal clearance is between 0.18 - 0.3 l/h.kg and total body clearance between 0.48 - 0.60 l/h.kg. Approximately 1% of a ciprofloxacin dose is excreted via the biliary route. The elimination kinetics are linear and after repeated dosing at 12 hourly intervals, no further accumulation is detected after the distribution equilibrium is attained (at 4-5 half-lives). The elimination half-life of unchanged ciprofloxacin over a period of 24-48 hours post-dose is 3.1-5.1 hours.

Some studies carried out with ciprofloxacin in severely renally impaired patients (serum creatinine>265 micromole/l or creatinine clearance <20ml/minute) demonstrated either a doubling of the elimination half-life, or fluctuations in half-life in comparison with healthy volunteers, whereas other studies showed no significant correlation between elimination half-life and creatinine clearance. However, it is recommended that in severely renally impaired patients, the total daily dose should be reduced by half, although monitoring of drug serum levels provides the most reliable basis for dose adjustment as necessary.

Results of pharmacokinetic studies in paediatric cystic fibrosis patients have shown dosages of 20mg/kg orally twice daily or 10mg/kg iv three times daily are recommended to achieve plasma concentration/time profiles comparable to those achieved in the adult population at the currently recommended dosage regimen.

Inhalation anthrax: Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for the recommended doses.

Indication(s):
Consideration should be given to available official guidance on the appropriate use of 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
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)
Selective intestinal decontamination in immunosuppressed patients

*Ificipro 250/500 should be only used:
- When Pseudomonas is considered AND the patient is allergic to antipseudomonal penicillins/cephalosporins;
- For resistant organisms with no other alternative antibiotics available.

Dosage and method of administration
General dosage recommendations: The dosage of Ificipro 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. Ificipro tablets should be swallowed whole with an adequate amount of liquid.
If Ificipro Tablets are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, the tablets should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt, and calcium fortified orange juice). However, a normal diet that will contain small amounts of calcium, does not significantly affect ciprofloxacin absorption. If the patient is unable to take tablets, because of the severity of the illness or for other reasons, it is recommended to commence the therapy with an intravenous form of ciprofloxacin.

1.1 Respiratory tractinfection (according to severity and organism)	2 x250 -500mg
1.2 Urinary tractinfections: -Acute, uncomplicated -Cystitisinwomen (beforemenopause) -Complicated	2x125mg 1-2x250 mg Singledose 250mg 2x250 -500mg
1.3 Gonorrhea -Extragenital -Acute, uncomplicated	2 x125mg Singledose 250mg
1.4 Diarrhea	1-2 x500mg
1.5 Otherinfections(see indications)	2x500mg
1.6 Particularly severe, life threatening infectionsi.e. -Streptococcal Pneumonia -Recurrentinfectionsin cysticfibrosis -Boneandjointinfections -Septicemia -Peritonitis In particular when Pseudomonas, Staphylocoocusor Streptococcus is present	2 x 750mg

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: 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.

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In streptococcal infections the treatment must last at least 10 days because of the risk of late complications. Infections caused by Chlamydia should also be treated for a minimum of 10 days.

Elderly: Elderly patients should receive a dose as low as possible depending on the severity of their illness and the creatnine clearance.

Renal and Hepatic impairment:
Impaired Renal Function: where creatinine clearance is between 31 and 60ml/min/1.73m2 or where the serum creatinine concentration is between 1.4 and 1.9mg/100ml. the maximum daily dose should be 1000mg per day for oral administration.
Where creatinine clearance is equal or is less than 30ml/min/1.73m2 or where the serum creatinine concentration is equal or higher than 2mg/100ml the maximum daily dose should be 500mg/day for oral administration.

Impaired renal function+ Haemodialysis:
Dose as in 1.2; on dialysis days after dialysis.

Impaired renal function + CAPD:
Administration of ciprofloxacin film coated tablets a 1x500mg film coated tablets or 2x250 mg film coated tablets.

Impaired Renal function: No dose adjustment is required.

Impaired Renal and Lever function: Dose adjustment as in 1.1 and 1.2.

Mode of Administration:
Tablet for oral consumption

Contraindication:
Ificipro is contraindicated in individuals with a history of hypersensitivity to Ciprofloxacin or any other quinolone derivative. Its use is not recommended in children below the age of 12 years.

Warning:
The on set of tendon pain calls for immediate withdrawal of this drug.

Precautions:
As Ificipro may cause CNS stimulation. It should be used with caution in patients with CNS disorders such as severe cerebral arteriosclerosis or epilepsy. Patients receiving this drugs should be well hydrated to prevent crystalluria. Excessive alkalinization of urine should be avoided. The dosage should be reduced in patients with renal impairment. Reproduction studies in animals at doses up to 6 times the usual daily human dose have not revealed any evidence of impaired fertility or teratogenicity due to Ificipro. However, information from well-controlled studies in pregnant women is not available. Since Ificipro causes arthropathy in immature animals, it should not be used in pregnant and nursing women.

The use of ciprofloxacin solution for infusion should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolones containing products (see section Adverse Effects/Undesirable Effects). Treatment of these patients with ciprofloxacin solution for infusion should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.

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. Marian 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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions
Very rare cases of prolonged (continuing months of 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. Ciprofloxacin should be discontinued immediately at the first signs or symptoms of any serious adverse reactions and patients should be advised to contact their prescriber for advice.

Exacerbation of myasthenia gravis
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

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 Ificipro Injection 200mg/100ml 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 paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with ciprofloxacin 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 (see section Adverse Effects/Undesirable Effects).

Interactions with Other Medicaments:
Serum concentrations and elimination half-life of theophylline may be increased when it is used concurrently with Ificipro it is recommended that patients be monitored for the signs of theophylline toxicity during concurrent use and dosage adjustments made as appropriate. Probenecid delays excretion of Ificipro.

Pregnancy and Lactation:
The safety and efficacy of ciprofloxacin in children, adolescents, pregnant women and lactating women have not been established.

Side Effects:
Ificipro (Ciprofloxacin) is generally well tolerated. During clinical trials in a large number of patients, adverse effects related to drug occurred infrequently and were commonly reported as diarrhoea, vomiting, abdominal pain, headache, restlessness and rash.

Other side effects which have been reported very rarely include arthralgia and increases in serum transaminases levels.

"Musculoskeletal and connective tissue disorders *

Nervous system disorders*

General disorders and administrative site conditions*

Psychiatric disorders*

Eye disorders*

Ear and labyrinth disorders*

*Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, 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 (see section Warnings and Precautions)."

Exacerbation of myasthenia gravis
Post Marketing Experience

Symptoms and Treatment of Overdosage:
Based on the limited information available in two cases of ingestion of over 18g of ciprofloxacin, reversible renal toxicity has occurred. Therefore, apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients must be kept well hydrated, and in the case of renal damage resulting in prolonged oliguria, dialysis should be initiated.
Serum levels of ciprofloxacin are reduced by dialysis.

Storage Conditions:
Store at a temperature not exceeding 30°C.

Shelf Life:
3 years from the month of manufacturer

Presentation:
Ificipro 250 mg tablets: 10 x10 Alu/PVC Strip
Ificipro 500 mg tablets: 10 x10 Alu/PVC Strip

Manufactured by:
Unique Pharmaceutical Laboratories
(A Div. Of J.B. Chemicals & Pharmaceuticals Limited)
Plot No. 215 – 219, G.I.D.C. Industrial Area, Panoli,
Dist. Bharuch, 394 116, India.
*Trade Mark

Product Registration Holder and Imported by:
Unimed SDN BHD
53, Jalan Tembaga SD 5/2B, B
andar Sri Damansara, 52200,
Kuala Lumpur

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