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

Ciprofloxacin Hydrochloride Tablets IP 250 mg / 500 mg

CIPROFLAV™ - 250 / 500

Composition:
Each film coated tablet contains:
Ciprofloxacin Hydrochloride IP
Eq. to Ciprofloxacin..... 250 mg
Colour : Titanium Dioxide IP

Composition:
Each film coated tablet contains:
Ciprofloxacin Hydrochloride IP
Eq. to Ciprofloxacin..... 500 mg
Colour : Titanium Dioxide IP

PHARMACEUTICAL FORM
Film Coated Tablet

THERAPEUTIC INDICATION
It is indicated for the treatment of respiratory tract infection, UTI, skin & soft tissue infection, severe systemic infections, surgical, gynae, G.I, bone & joint infections, STD.

DOSAGE AND ADMINISTRATION
Posology
The dosage is determined by the indication, the severity and the site of the infection, the susceptibility to ciprofloxacin of the causative organism(s), the renal function of the patient and, in children and adolescents the body weight.
The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.
Treatment of infections due to certain bacteria (e.g. Pseudomonas aeruginosa, Acinetobacter or Staphylococci) may require higher ciprofloxacin doses and co-administration with other appropriate antibacterial agents.
Treatment of some infections (e.g. pelvic inflammatory disease, intra-abdominal infections, infections in neutropenic patients and infections of bones and joints) may require co-administration with other appropriate antibacterial agents depending on the pathogens involved.
Adults: The recommended adult oral dosage of Ciprofloxacin tablet is 250 mg - 750 mg twice daily depending upon the severity of infection or as directed by the Physician.
Paediatric population: The recommended adult oral dosage of Ciprofloxacin tablet is 10-20 mg/kg body weight twice daily depending upon the severity of infection or as directed by the Physician.
The maximum daily dose of Ciprofloxacin for pediatric patients, 750 mg per dose in severe infections and less than 500 mg per dose in mild to moderate infections.
Elderly Patients: Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.
Renal and hepatic impairment: Recommended starting and maintenance doses for patients with impaired renal function:

Creatinine clearance (mL/min/1.73 m²)	Serum creatinine (µmol/L)	Oral Dose (mg)
> 60	< 124	Usual Dosage
30-60	124 to 168	250-500 mg every 12 h
< 30	> 169	250-500 mg every 24 h
Patients on haemodialysis	> 169	250-500 mg every 24 h (after dialysis)
Patients on peritoneal dialysis	> 169	250-500 mg every 24 h

In patients with impaired liver function no dose adjustment is required.
Dosing in children with impaired renal and/or hepatic function has not been studied.
Method of administration: For oral administration only.
Patients should be advised to swallow the tablet whole with liquid and must not be chewed or crushed. They can be taken independent of meal times. If taken on an empty stomach, the active substance is absorbed more rapidly. Ciprofloxacin tablets should not be taken with dairy products (e.g. milk, yoghurt) or mineral-fortified fruit-juice (e.g. calcium-fortified orange juice).
In severe cases or if the patient is unable to take tablets (e.g. patients on enteral nutrition), it is recommended to commence therapy with intravenous ciprofloxacin until a switch to oral administration is possible.

CONTRAINDICATIONS
It is contraindicated in patients with known hypersensitivity to the active substance, to other quinolones or to any of the excipients.
• Concomitant administration of ciprofloxacin and tizanidine.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population.
Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).
In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.
The use of Ciprofloxacin should be avoided in patients who have experienced serious adverse reactions in the past when using quinolone or fluoroquinolone containing products. Treatment of these patients with Ciprofloxacin should only be initiated in the absence of alternative treatment options and after careful benefit/risk assessment.
Severe infections and mixed infections with Gram-positive and anaerobic pathogens
Ciprofloxacin monotherapy is not suited for treatment of severe infections and infections that might be due to Gram-positive or anaerobic pathogens. In such infections ciprofloxacin must be co-administered with other appropriate antibacterial agents.
Streptococcal Infections (including *Streptococcus pneumoniae)*
Ciprofloxacin is not recommended for the treatment of streptococcal infections due to inadequate efficacy.
Genital tract infections
Gonococcal urethritis, cervicitis, epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae isolates. Therefore, ciprofloxacin should be administered for the treatment of gonococcal uretritis or cervicitis only if ciprofloxacin-resistant Neisseria gonorrhoeae can be excluded.
Urinary tract infections
Resistance to fluoroquinolones of Escherichia coli - the most common pathogen involved in urinary tract infections – varies across the European Union. Prescribers are advised to take into account the local prevalence of resistance in Escherichia coli to fluoroquinolones.
The single dose of ciprofloxacin that may be used in uncomplicated cystitis in pre-menopausal women is expected to be associated with lower efficacy than the longer treatment duration. This is all the more to be taken into account as regards the increasing resistance level of Escherichia coli to quinolones.
Paediatric population
The use of ciprofloxacin in children and adolescents should follow available official guidance.
Ciprofloxacin treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents.
Broncho-pulmonary infections in cystic fibrosis: Clinical trials have included children and adolescents aged 5-17 years. More limited experience is available in treating children between 1 and 5 years of age.
Complicated urinary tract infections and pyelonephritis: Ciprofloxacin treatment of urinary tract infections should be considered when other treatments cannot be used, and should be based on the results of the microbiological documentation.
Clinical trials have included children and adolescents aged 1-17 years.
Other specific severe infections: Other severe infections in accordance with official guidance, or after careful benefit-risk evaluation when other treatments cannot be used, or after failure to conventional therapy and when the microbiological documentation can justify ciprofloxacin use.
The use of ciprofloxacin for specific severe infections other than those mentioned above has not been evaluated in clinical trials and the clinical experience is limited. Consequently, caution is advised when treating patients with these infections.
Hypersensitivity
Hypersensitivity and allergic reactions, including anaphylaxis and anaphylactoid reactions, may occur following a single dose and may be life-threatening. If such reaction occurs, ciprofloxacin should be discontinued and an adequate medical treatment is required.
Musculoskeletal System
Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed to these patients for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with quinolones and fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients, patients with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided. At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Ciprofloxacin should be discontinued and alternative treatment should be considered. The affected limb(s) should be appropriately treated (e.g. immobilisation). Corticosteroids should not be used if signs of tendinopathy occur.
Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be aggravated.
Photosensitivity
Ciprofloxacin has been shown to cause photosensitivity reactions. Patients taking ciprofloxacin should be advised to avoid direct exposure to either extensive sunlight or UV irradiation during treatment.
Cardiac disorders
Caution should be taken when using fluoroquinolones, including ciprofloxacin, in patients with known risk factors for prolongation of the QT interval such as, for example:
- Congenital long QT syndrome
- Concomitant use of drugs that are known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics)
- uncorrected electrolyte imbalance (e.g. hypokalaemia, hypomagnesaemia)
- Cardiac disease (e.g. heart failure, myocardial infarction, bradycardia) Elderly patients and women may be more sensitive to QTc-prolonging medications. Therefore, caution should be taken when using fluoroquinolones, including ciprofloxacin, in these populations.

Dysglycaemia
As with all quinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g., glibenclamide) or with insulin. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended.
Gastrointestinal System
The occurrence of severe and persistent diarrhoea during or after treatment (including several weeks after treatment) may indicate an antibiotic-associated colitis (life-threatening with possible fatal outcome), requiring immediate treatment. In such cases, ciprofloxacin should immediately be discontinued, and an appropriate therapy initiated. Anti-peristaltic drugs are contraindicated in this situation.
Renal and urinary system
Crystalluria related to the use of ciprofloxacin has been reported. Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.
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.
Resistance
During or following a course of treatment with ciprofloxacin bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudomonas species.
Cytochrome P450
Ciprofloxacin inhibits CYP1A2 and thus may cause increased serum concentration of concomitantly administered substances metabolised by this enzyme (e.g. theophylline, clozapine, olanzapine, ropinirole, tizanidine, duloxetine, agomelatine). Co-administration of ciprofloxacin and tizanidine is contra-indicated. Therefore, patients taking these substances concomitantly with ciprofloxacin should be monitored closely for clinical signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be necessary.
Interaction with tests
The in-vitro activity of ciprofloxacin against Mycobacterium tuberculosis might give false negative bacteriological test results in specimens from patients currently taking ciprofloxacin.
Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesia, hypaesthesia, dysesthesia, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with [INN] should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop in order to prevent the development of potentially irreversible condition. Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and fluoroquinolones irrespective of their age and pre-existing risk factors. [INN] should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

DRUG INTERACTION
Effects of other products on ciprofloxacin:
Drugs known to prolong QT interval: Ciprofloxacin, like other fluoroquinolones, should be used with caution in patients receiving drugs known to prolong QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).
Chelation Complex Formation: The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing drugs and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, or calcium reduces the absorption of ciprofloxacin. 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 H2 receptor blockers.
Food and Dairy Products: Dietary calcium as part of a meal does not significantly affect absorption. However, the concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) with ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced.
Probenecid: Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid and ciprofloxacin increases ciprofloxacin serum concentrations.
Metoclopramide: Metoclopramide accelerates the absorption of ciprofloxacin (oral) resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.
Omeprazole: Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of Cmax and AUC of ciprofloxacin
Effects of ciprofloxacin on other medicinal products:
Tizanidine: Tizanidine must not be administered together with ciprofloxacin. In a clinical study with healthy subjects, there was an increase in serum tizanidine concentration (Cmax increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Increased serum tizanidine concentration is associated with a potentiated hypotensive and sedative effect.
Methotrexate: Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.
Theophylline: Concurrent administration of ciprofloxacin and theophylline can cause an undesirable increase in serum theophylline concentration. This can lead to theophylline-induced side effects that may rarely be life threatening or fatal. During the combination, serum theophylline concentrations should be checked and the theophylline dose reduced as necessary.
Other xanthine derivatives: On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these xanthine derivatives were reported.
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.
Ciclosporin: A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and ciclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.
Vitamin K antagonists: Simultaneous administration of ciprofloxacin with a vitamin k antagonist may augment its anti-coagulant effects. There have been many reports of increases in oral anticoagulant activity in patients receiving antibacterial agents, including fluoroquinolones. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of the fluoroquinolone to the increase in INR (international normalised ratio) is difficult to assess. It is recommended that the INR should be monitored frequently during and shortly after co-administration of ciprofloxacin with a vitamin k antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione).
Duloxetine: In clinical studies, it was demonstrated that concomitant use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no clinical data are available on a possible interaction with ciprofloxacin, similar effects can be expected upon concomitant administration.
Ropinirole: It was shown in a clinical study that concomitant use of ropinirole with ciprofloxacin, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase of Cmax and AUC of ropinirole by 60% and 84%, respectively. Monitoring of ropinirole-related side effects and dose adjustment as appropriate is recommended during and shortly after co-administration with ciprofloxacin.
Lidocaine: It was demonstrated in healthy subjects that concomitant use of lidocaine containing medicinal products with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22%. 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 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after coadministration with ciprofloxacin are advised.
Sevelamer: The bioavailability of ciprofloxacin is reduced by the concomitant administration with sevelamer (up to 50%), therefore, it is recommended that the two should not be taken concomitantly.
Sildenafil: Cmax and AUC of sildenafil were increased approximately twofold in healthy subjects after an oral dose of 50 mg given concomitantly with 500 mg ciprofloxacin. Therefore, caution should be used prescribing ciprofloxacin concomitantly with sildenafil taking into consideration the risks and the benefits.
Agomelatine: In clinical studies, 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.

USE IN SPECIAL POPULATION
Pregnancy
Pregnancy category: C. There are no adequate and well-controlled studies in pregnant women.
The data that are available on administration of ciprofloxacin to pregnant women indicates no malformative or foeto/neonatal toxicity of ciprofloxacin. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. In juvenile and prenatal animals exposed to quinolones, effects on immature cartilage have been observed, thus, it cannot be excluded that the drug could cause damage to articular cartilage in the human immature organism / foetus. As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.
Breast-feeding
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, ciprofloxacin should not be used during breast-feeding.
Pediatric Use
Although effective in clinical trials, Ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to controls. Quinolones, including Ciprofloxacin, cause arthropathy in juvenile animals.
Complicated Urinary Tract Infection and Pyelonephritis: Ciprofloxacin is indicated for the treatment of cUTI and pyelonephritis due to Escherichia coli in pediatric patients 1 to 17 years of age. Although effective in clinical trials, Ciprofloxacin is not a drug of first choice in the pediatric population due to an increased incidence of adverse reactions compared to the controls, including events related to joints and/or surrounding tissues.
Inhalational Anthrax (Post-Exposure): Ciprofloxacin is indicated in pediatric patients from birth to 17 years of age, for inhalational anthrax (post-exposure). The risk-benefit assessment indicates that administration of ciprofloxacin to pediatric patients is appropriate.
Plague: Ciprofloxacin is indicated in pediatric patients from birth to 17 years of age, for treatment of plague, including pneumonic and septicemic plague due to Yersinia pestis (Y. pestis) and prophylaxis for plague. Efficacy studies of Ciprofloxacin could not be conducted in humans with pneumonic plague for feasibility reasons. Therefore, approval of this indication was based on an efficacy study conducted in animals. The risk benefit assessment indicates that administration of Ciprofloxacin to pediatric patients is appropriate.
Elderly Patients
Elderly patients should receive a dose selected according to the severity of the infection and the patient's creatinine clearance.
Renal Impairment
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.
Hepatic Impairment
In preliminary studies in patients with stable chronic liver cirrhosis, no significant changes in ciprofloxacin pharmacokinetics have been observed. The pharmacokinetics of ciprofloxacin in patients with acute hepatic insufficiency, have not been studied.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Due to its neurological effects, ciprofloxacin may affect reaction time. Thus, the ability to drive or to operate machinery may be impaired.

UNDESIRABLE EFFECTS/ADVERSE DRUG REACTION
Ciprofloxacin induced Stevenson Johnson Syndrome (SJS)/Toxic Epidermal Necrosis (TEN)
Low blood sugar and mental health related side effects:
The drug may cause low blood sugar and mental health related side effects. Low blood sugar levels, also called as hypoglycemia, can lead to coma. The mental health side effects more prominent and more consistent across the systemic fluoroquinolone drug class. The mental side effects to fluoroquinolones are:
• Disturbance in attention,
• Disorientation,
• Agitation,
• Nervousness,
• Memory impairment,
• Serious disturbances in mental abilities called delirium.
Summary of the safety profile
The most commonly reported adverse drug reactions (ADRs) are nausea and diarrhoea.
ADRs derived from clinical studies and post-marketing surveillance with Ciprofloxacin (oral, intravenous, and sequential therapy) sorted by categories of frequency are listed below. The frequency analysis takes into account data from both oral and intravenous administration of ciprofloxacin.
Estimated frequencies of reactions are ranked according to the following convention: common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).
Infections and Infestations: Uncommon: Mycotic superinfections.
Blood and Lymphatic System Disorders: Uncommon: Eosinophilia. Rare: Leukopenia, Anaemia, 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. Rare: Hyperglycaemia, Hypoglycaemia. Frequency not known: Hypoglycaemic coma.
Psychiatric Disorders: Uncommon: Psychomotor hyperactivity / agitation. Rare: Confusion and disorientation, Anxiety reaction, Abnormal dreams, Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide), Hallucinations. Very Rare: Psychotic reactions (potentially culminating in suicidal ideations/ thoughts or suicide attempts and completed suicide). Frequency not known: Mania, hypomania.
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, Gait disturbance, Olfactory nerve disorders, Intracranial hypertension, Pseudotumor cerebri. Frequency not known: Peripheral neuropathy and polyneuropathy.
Eye Disorders: Rare: Visual disturbances (e.g. diplopia), Very rare: Visual colour distortions.
Ear and Labyrinth Disorders: Rare: Tinnitus, Hearing loss / Hearing impaired.
Cardiac Disorders: Rare: Tachycardia. Frequency not known: Ventricular arrhythmia and torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged.
Vascular Disorders: Rare: Vasodilatation, Hypotension, Syncope. Very rare: Vasculitis.
Respiratory, Thoracic and Mediastinal Disorders: Rare: Dyspnoea (including asthmatic condition).
Gastrointestinal Disorders: Common: Nausea, Diarrhoea. Uncommon: Vomiting, Gastro-intestinal and abdominal pains, Dyspepsia, Flatulence. Very rare: Pancreatitis.
Hepatobiliary Disorders: Uncommon: Increase in transaminases, increased bilirubin. Rare: Hepatic impairment, Cholestatic icterus, Hepatitis. Very rare: Liver necrosis (very rarely progressing to life- threatening hepatic failure).
Skin and Subcutaneous Tissue Disorders: Uncommon: Rash, Pruritus, and Urticaria. Rare: Photosensitivity reactions. Very rare: Petechiae, Erythema multiforme, Erythema nodosum, Stevens-Johnson syndrome (potentially life- threatening), Toxic epidermal necrolysis (potentially life- threatening). Frequency not known: Acute generalised exanthematous pustulosis (AGEP), DRESS (Drug reaction with eosinophilia and systemic symptoms) syndrome.
Musculo- skeletal, Connective Tissue and Bone Disorders: Uncommon: Musculoskeletal pain (e.g. extremity pain, back pain, chest pain), 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, Haematuria, Crystalluria, Tubulointerstitial nephritis.
General Disorders and Administration Site Conditions: Uncommon: Asthenia, Fever. Rare: Oedema, Sweating (hyperhidrosis).
Investigations: Uncommon: Increase in blood alkaline phosphatase. Rare: Increased amylase. Frequency not known: International normalised ratio increased (in patients treated with Vitamin K antagonists).
Endocrine disorders: Frequency not known: Syndrome of inappropriate secretion of antidiuretic hormone (SIADH).
Paediatric population
The incidence of arthropathy, mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly.

OVERDOSE
An overdose of 12 g has been reported to lead to mild symptoms of toxicity. An acute overdose of 16 g has been reported to cause acute renal failure.
Symptoms in overdose consist of dizziness, tremor, headache, tiredness, seizures, hallucinations, confusion, abdominal discomfort, renal and hepatic impairment as well as crystalluria and haematuria.
Reversible renal toxicity has been reported.
Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patients should be kept well hydrated. Only a small quantity of ciprofloxacin (<10%) is eliminated by haemodialysis or peritoneal dialysis.
In the event of overdose, symptomatic treatment should be implemented. ECG monitoring should be undertaken, because of the possibility of QT interval prolongation.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: fluoroquinolones.
Ciprofloxacin is a second generation fluoroquinolone that is active against many Gram negative and Gram positive bacteria. It produces its action through inhibition of bacterial DNA gyrase and topoisomerase IV. Ciprofloxacin binds to bacterial DNA gyrase with 100 times the affinity of mammalian DNA gyrase. There is no cross resistance between fluoroquinolones and other classes of antibiotics, so it may be of clinical value when other antibiotics are no longer effective. Ciprofloxacin and its derivatives are also being investigated for its action against malaria, cancers, and AIDS. Ciprofloxacin acts on bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. Ciprofloxacin's targeting of the alpha subunits of DNA gyrase prevents it from supercoiling the bacterial DNA which prevents DNA replication.
Mechanism of action
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.
PK/PD relationship
Efficacy mainly depends on the relation between the maximum concentration in serum (Cmax) 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.

Pharmacokinetic properties
Absorption
After oral administration, ciprofloxacin is predominantly absorbed from the duodenum and upper jejunum, and reaches peak serum concentrations within 60-90 min. After single doses of 250mg and 500mg Cmax values are about 0.8-2.0mg/1 and 1.5-2.9mg/1 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 2-3 l/kg. Since the protein binding of ciprofloxacin is low (20-30%) and the substance is predominantly present in the blood plasma in non-ionised form, almost the entire quantity of the administered dose can diffuse freely into the extravasal space. As a result, the concentrations in certain body fluids and tissues may be markedly higher than the corresponding serum concentrations.
Metabolism / Elimination
Ciprofloxacin is essentially excreted in unchanged form, mostly in the urine. Renal clearance lies between 3 and 5ml/min/kg, and total clearance amounts to 8-10ml/min/kg. Both glomerular filtration and tubular secretion play a part in the elimination of ciprofloxacin.
Small concentrations of 4 metabolites were found: desethylene ciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). M 1 to M 3 show antibacterial activity comparable with or smaller than nalidixic acid. M 4 with the lowest quantity, has an antimicrobial activity very much corresponding to norfloxacin.
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.

INCOMPATIBILITY
Not applicable.

SHELF LIFE
24 months

STORAGE INSTRUCTIONS
Store protected from light & moisture, at a temperature not exceeding 30°C.

Keep all medicines out of reach of children.

PACKAGING INFORMATION
Pack of 20 blisters of 10 tablets with line cut and packed in a carton along with package insert.

Mfg. Lic. No.: 4/UA/LL/2014

Manufactured by:
Akums Drugs & Pharmaceuticals Ltd.
At: Plot No. 26A, 27-30, Sector-8A, I.I.E., SIDCUL,
Ranipur, Haridwar-249 403, Uttarakhand.

Marketed by:
Mylan Pharmaceuticals Private Limited
Plot No. 564/A/22, Road No. 92,
Jubilee Hills, Hyderabad,
Telangana-500096.

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