Axcel®

CIPROFLOXACIN-250mg

TABLET

MAL13115208AZ

COMPOSITION:
Each tablet contains
Ciprofloxacin Hydrochloride
equivalent to Ciprofloxacin 250mg

PRESENTATION:
Round shaped, white color film-coated tablet debossed with the KOTRA logo on one side and score line on the reverse side.

INDICATIONS:
Consideration should be given to 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 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*.

*Axcel Ciprofloxacin Tablet should be only used:
- When Pseudomonas is considered AND patient is allergic to antipseudomonal penicillins / cephalosporins;
- 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. The clinical trials in children were performed in the indications listed above. For other indications clinical experience is limited.

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

PHARMACOLOGY:
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 (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 when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. Groupings of relevant species according to ciprofloxacin susceptibility (for *Streptococcus* species see '*Warning & Precautions*').

Commonly susceptible organisms:
Aerobic Gram-positive micro-organisms : *Bacillus anthracis* (1)

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.** (2).

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.*

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.
+Resistance rate ≥ 50% in one or more EU countries.
($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance.
(1): Studies have been conducted in experimental animal infections due to inhalations of *Bacillus anthracis* spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on *in-vitro* susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 500mg bid, is considered as effective to prevent anthrax infection in humans. The treating physician should refer to national and / or international consensus documents regarding treatment of anthrax.
(2): Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50% among all staphylococcal species and is usually higher in nosocomial isolates.

Pharmacokinetics:
Absorption:
Following oral administration of single doses of 250mg, 500mg, and 750mg of Ciprofloxacin tablets, Ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. Single doses of 100-750mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7mg/L. Serum concentrations increase proportionately with doses up to 1000mg. The absolute bioavailability is approximately 70-80%. A 500mg 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 400mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution:
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 iso-enzymes.

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.

Excretion of Ciprofloxacin (% of Dose) - Oral Administration		
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M1-M4)	11.3	7.5

Renal clearance is between 180-300mL/kg/h and the total body clearance is between 480-600mL/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 h. 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. In a study 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 (10mg/kg three times daily) was observed. In 10 children with severe sepsis C_{max} was 6.1mg/L (range 4.6-8.3mg/L) after a 1-hour intravenous infusion of 10mg/kg in children aged less than 1 year compared to 7.2mg/L (range 4.7-11.8mg/L) for children between 1 and 5 years of age. The AUC values were 17.4mg*h/L (range 11.8-32.0mg*h/L) and 16.5mg*h/L (range 11.0-23.8mg*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%.

DOSAGE AND ADMINISTRATION:
For oral administration only, independent of mealtime. If the tablets are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, tablets should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. milk, yoghurt and calcium fortified orange juice). 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. After intravenous administration the treatment can be continued orally.

Unless otherwise prescribed, the following guideline doses are recommended for :

Adults:

Indications	Recommended Dosage (Tablets)
Infections of the respiratory tract I (according to severity and organism)	2 x 500mg to 2 x 750mg
Urinary tract infections: - acute, uncomplicated - cystitis in women (before menopause) - complicated	 2 x 250mg to 2 x 500mg single dose 500mg 2 x 500mg to 2 x 750mg
Genital infections: - uncomplicated gonorrhea (including extragenital sites of infection) - adnexitis, prostatitis, epididymo-orchitis	 1 x 500mg 2 x 500mg to 2 x 750mg
Diarrhea	2 x 500mg
Other infections (see Indications)	2 x 500mg
Particularly severe, life threatening infections such as : - 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

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.

Additional information on special patient population:
Children and adolescents:

Indications	Recommended Dosage (Tablets)
Infections in cystic fibrosis	2 × 20mg/kg body weight (maximum of 750 mg per dose)
Complicated urinary tract infections and pyelonephritis	2 × 10mg/kg body weight to 2 × 20mg/kg body weight (maximum of 750 mg per dose)
Inhalational anthrax (post-exposure)	2 × 15mg/kg body weight (maximum of 500mg per dose)

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.

Patients with renal and hepatic impairment:
Adults:
• 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 60mL/min/1.73m² (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9mg/100 mL, 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/100 mL, the maximum daily oral dose of Ciprofloxacin should be 500mg 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 film- coated tablet or 2 x 250mg film-coated tablets).

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

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
• and 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* 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.

CONTRAINDICATION:
Hypersensitivity to Ciprofloxacin or other quinolone or any of the excipients. Concurrent administration of Ciprofloxacin and Tizanidine (see '*Drug Interaction*').

WARNING AND PRECAUTION:
The use of Ciprofloxacin should be avoided in patients who have experienced serious adverse reaction in the past when using fluoroquinolones containing products (see section '*Side Effects*'). 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 / or infections due to Gram-positive or anaerobic bacteria:
For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, Ciprofloxacin should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections:
Ciprofloxacin is not recommended for treatment of pneumococcal infections due to limited 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:
As with medicinal products in its class, 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.

Hypersensitivity:
In some instances, hypersensitivity and allergic reactions may occur following a single dose, a physician should be informed immediately. Anaphylactic/anaphylactoid reactions in very rare instances can progress to a life-threatening shock, in some instances after the first administration. In these cases, Ciprofloxacin has to be discontinued and medical treatment (e.g. treatment for shock) is required.

Gastrointestinal system:
In the event of severe and persistent diarrhea during or after treatment, a physician 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, Ciprofloxacin must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250mg/day). Medicinal products that inhibit peristalsis are contraindicated in this situation.

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 Ciprofloxacin.

Prolonged, disabling and potentially irreversible serious adverse drug reactions:
Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse 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 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.

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.

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

Seizures:
Ciprofloxacin 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, Ciprofloxacin should be discontinued.

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, Ciprofloxacin should be discontinued and appropriate measures instituted. Caution is recommended if Ciprofloxacin is to be used in psychotic patients or in patients with a history of psychiatric disease.

Peripheral neuropathy:
Cases of sensory or sensorimotor polyneuropathy resulting in paresthesias, hypoesthesias, dysesthesias, or weakness have been reported in patients receiving quinolones and fluoroquinolones. Patients under treatment with Ciprofloxacin should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop.

Skin and appendages:
Ciprofloxacin has been shown to produce photosensitivity reactions. Patients taking Ciprofloxacin should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitization (i.e. sunburn-like skin reactions) occurs.

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.

Dysglycemia:
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Ciprofloxacin. In Ciprofloxacin - 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.

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 Ciprofloxacin.

Effects on ability to drive and use machines:
Fluoroquinolones including ciprofloxacin may result in an impairment of the patient's ability to drive or operate machinery due to CNS reactions. This applies particularly in combination with alcohol.

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 Ciprofloxacin 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 the potential risk of articular damage, the use of Ciprofloxacin is not recommended during breast-feeding.

SIDE EFFECTS:
The frequencies of ADRs reported with Ciprofloxacin are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. The ADRs identified only during post-marketing surveillance, and for which a frequency could not be estimated, are listed under "not known".

System Organ Class	Common ≥ 1% to < 10%	Uncommon ≥ 0.1% to < 1%	Rare ≥ 0.01% to < 0.1%	Very rare < 0.01%	Not Known (cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia, Anemia Neutopenia, Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anemia Agranulocytosis Pancytopenia (life - threatening) Bone marrow depression (life - threatening)	
Immune System Disorders			Allergic reactions Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness - like reaction	
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycemia Hypoglycemia		
Cardiac Disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de pointes *
Eye Disorders #		Visual disturbances	Visual color distortions		
Psychiatric Disorders #		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide)	
Nervous System Disorders #		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysesthesia Hypoesthesia, Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumor cerebri)	Peripheral neuropathy and polyneuropathy
Ear and Labyrinth Disorders #		Tinnitus, Hearing loss	Hearing impaired		
Vascular Disorders			Vasodilatation, Syncope Hypotension	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnea (including asthmatic condition)		
Gastrointestinal	Nausea Diarrhoea	Vomiting Gastrointestinal		Pancreatitis	
Disorders		Gastrointestinal and abdominal pains Dyspepsia, Flatulence			
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Hepatitis (non infective)	Liver necrosis (very rarely progressing to life-threatening hepatic failure)	
Skin and Subcutaneous Tissue Disorders		Rash, Pruritus, Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)	Acute generalized exanthematous pustulosis (AGEP)
Musculoskeletal, Connective Tissue and Bone Disorders #		Arthralgia	Myalgia, Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis, Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis	
Renal and Urinary Disorders		Renal impairment	Renal failure, Hematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions #		Unspecific pain Feeling unwell, Fever	Eedema Sweating (hyperhidrosis)	*Gait disturbance*	
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase	International normalized ratio (INR) increased (in patients treated with Vitamin K antagonists)	

*These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see 'Special warnings and precautions for use').
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).
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 intravenous or 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, Eedema
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 data collected in studies with adults. In children, arthropathy is reported to occur commonly (see '*Warning and Precautions*').

DRUG INTERACTION:
Drugs known to prolong QT interval:
Ciprofloxacin, like other fluroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics).

Chelation complex formation:
The simultaneous administration of Ciprofloxacin and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminum, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminum, or calcium reduce 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:
The concurrent administration of dairy products or mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) and Ciprofloxacin should be avoided because absorption of ciprofloxacin may be reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

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

Metoclopramide:
Metoclopramide accelerates the absorption of ciprofloxacin 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 C_{max} and AUC of ciprofloxacin.

Tizanidine:
In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) 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 Ciprofloxacin.

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

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

Phenytoin:
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving Ciprofloxacin and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related undesirable effects when Ciprofloxacin 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 Ciprofloxacin with phenytoin.

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.

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 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 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 normalized ratio) is difficult to assess. 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 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:
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 C_{max} and AUC of ropinirole by 60% and 84%, respectively. Monitoring ropinirole-related undesirable effects 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 co-administration with Ciprofloxacin are advised.

Sildenafil:
C_{max} 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.

OVERDOSAGE & TREATMENT:
In the event of acute, excessive oral 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:
Store below 30°C. Protect from light.

KEEP OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

PACKAGE QUANTITIES:
Available in blister pack of 10 x 10's.

Further information can be obtained from pharmacist, physician or the manufacturer.

Manufactured By & Product Registration Holder :
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