

1.4 PRODUCT INFORMATION.

1.4.1 Prescribing Information (Summary of Product Characteristics): (Enclosed).

1. Name of the medicinal product

Ciprolab 500 Tablets.

2. Qualitative and quantitative composition

Each film coated tablet contains: Ciprofloxacin Hydrochloride USP (as Monohydrate) 500.0mg.

For more information on excipients see section 6.1

3.0 Pharmaceutical form: Tablet for oral administration.

White, circular, biconvex film coated tablets scored on one side and plain on reverse, packed in Alu/PVC blister packs of 10 x 10's contained in a unit box along with literature inserts.

4.0 Clinical particulars

4.1 Therapeutic indications

Ciprolab® tablets are used in treatment of uncomplicated, acute and chronic conditions/infections caused by or associated with pathogens sensitive to ciprofloxacin. These infections/conditions include, biliary-tract infections, bone and joint infections, brucellosis, cat scratch disease, chancroid, gastro-enteritis (including travellers' diarrhoea and chlorella, salmonella enteritis and shigellosis), gonorrhoea, meningitis, peritonitis, otitis externa, Q fever, lower respiratory tract infections, spotted fevers, typhoid and paratyphoid fever.

4.2 Posology and method of administration:

Method of administration: Oral administration.

Treatment Regimen:

The duration of treatment depends on the severity of illness and on the clinical and bacteriological course. The therapy should in principle be continued systematically for at least 3 days after disappearance of the clinical symptoms. In streptococcal infections, the treatment must be continued for at least 10 days because of the risk of late complications.

Diagnosis	Dosage	Duration of Therapy
Acute gonorrhoea and acute uncomplicated cystitis	250mg-500mg.	Single dose.
Uncomplicated upper and lower urinary tract infections	250mg twice daily.	7 days.
Complicated urinary tract infections	250-500mg twice daily.	7 days.
Respiratory tract infections (e.g bronchitis)	250-500mg twice daily.	7 days.
Prophylaxis of meningococcal meningitis	500mg.	Single dose.
Other infections/conditions (see the indications)	500mg twice daily.	7-14 days.

4.3 Contraindications

- Hypersensitivity to the active substance, to other quinolones or to any of the excipients listed in section 6.1.
- Concomitant administration of ciprofloxacin and tizanidine

4.4 Special warnings and precautions for use

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.

Prolonged, disabling and potentially irreversible serious adverse drug reactions:

Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse drug reactions affecting different, sometimes multiple, body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving quinolones and 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.

Aortic aneurysm and dissection, and heart valve regurgitation/incompetence:

Epidemiologic studies report an increased risk of aortic aneurysm and dissection, particularly in elderly patients, and of aortic and mitral valve regurgitation after intake of fluoroquinolones. Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones.

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 congenital heart valve disease, or in patients diagnosed with pre-existing aortic aneurysm and/or dissection or heart valve disease, or in presence of other risk factors or conditions predisposing:

- For both aortic aneurysm and dissection and heart valve regurgitation/incompetence (e. g. connective tissue disorders such as Marfan syndrome or Ehlers-Danlos syndrome, Turner syndrome, Behcet's disease, hypertension, rheumatoid arthritis) or additionally:
- For aortic aneurysm and dissection (e. g. vascular disorders such as Takayasu arteritis or giant cell arteritis, or known atherosclerosis, or Sjögren's syndrome) or additionally
- For heart valve regurgitation/incompetence (e. g. infective endocarditis).

The risk of aortic aneurysm and dissection, and their rupture may also be increased in patients treated concurrently with systemic corticosteroids.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately consult a physician in an emergency department.

Patients should be advised to seek immediate medical attention in case of acute dyspnoea, new onset of heart palpitations, or development of oedema of the abdomen or lower extremities.

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 coadministered 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 urethritis or cervicitis only if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin should only be considered in combination with another appropriate antibacterial agent (e. g. a cephalosporin) unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

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.

Intra-abdominal infections:

There are limited data on the efficacy of ciprofloxacin in the treatment of post-surgical intra-abdominal infections.

Travellers' diarrhoea:

The choice of ciprofloxacin should take into account information on resistance to ciprofloxacin in relevant pathogens in the countries visited.

Infections of the bones and joints:

Ciprofloxacin should be used in combination with other antimicrobial agents depending on the results of the microbiological documentation.

Inhalational anthrax:

Use in humans is based on in-vitro susceptibility data and on animal experimental data together with limited human data. Treating physicians should refer to national and/or international consensus documents regarding the treatment of anthrax.

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.

Ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals. Safety data from a randomised double-blind study on ciprofloxacin use in children (ciprofloxacin: n=335, mean age = 6.3 years; comparators: n=349, mean age = 6.2 years; age range = 1 to 17 years) revealed an incidence of suspected drug-related arthropathy (discerned from joint-related clinical signs and symptoms) by Day +42 of 7.2% and 4.6%. Respectively, an incidence of drug-related arthropathy by 1-year follow-up was 9.0% and 5.7%. The increase of suspected drug-related arthropathy cases over time was not statistically significant between groups. Treatment should be initiated only after a careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissue.

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 a 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.

Tendinitis and tendon rupture:

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 exacerbated.

Vision disorders:

If vision becomes impaired or any effects on the eyes are experienced, an eye specialist should be consulted immediately.

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.

Central Nervous System:

Ciprofloxacin like other quinolones are known to trigger seizures or lower the seizure threshold. Cases of non-convulsive status epilepticus have been reported. Ciprofloxacin should be used with caution in patients with CNS disorders which may be predisposed to seizure. If seizures occur ciprofloxacin should be discontinued. Psychiatric reactions may occur even after the first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to suicidal ideations/thoughts culminating in attempted suicide or completed suicide. In the occurrence of such cases, ciprofloxacin should be discontinued.

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 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.

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.

Impaired renal function:

Since ciprofloxacin is largely excreted unchanged via renal pathway dose adjustment is needed in patients with impaired renal

function to avoid an increase in adverse drug reactions due to accumulation of ciprofloxacin.

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.

Glucose-6-phosphate dehydrogenase deficiency:

Haemolytic reactions have been reported with ciprofloxacin in patients with glucose-6-phosphate dehydrogenase deficiency. Ciprofloxacin should be avoided in these patients unless the potential benefit is considered to outweigh the possible risk. In this case, potential occurrence of haemolysis should be monitored.

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.

Methotrexate:

The concomitant use of ciprofloxacin with methotrexate is not recommended.

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.

4.5 Interaction with other medicinal products and other forms of 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 the 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 or lanthanum carbonate), 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 C_{max} 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 (C_{max} 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.

Cyclosporin:

A transient increase in the concentration of plasma creatinine is seen when ciprofloxacin and cyclosporin are 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 vitamin K antagonists may augment its anti-coagulant effects. The risk may vary with the underlying infection, age and general status of the patient so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess. 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 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 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.

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 ('Cytochrome P450' in section 'Special warnings and precautions for use').

Zolpidem:

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

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.

4.6. Pregnancy and lactation

Pregnancy

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.

4.7 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.

4.8 Undesirable effects

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.

System Organ Class	Common ≥ 1/100 to < 1/10	Uncommon ≥ 1/1 000 to < 1/100	Rare ≥ 1/10 000 to < 1/1000	Very Rare < 1/10 000	Frequency not known (Cannot be estimated from available data)
Infections and Infestations		Mycotic superinfections			
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia, Anaemia, Neutropenia, Leukocytosis, Thrombocytopenia, Thrombocytæmia	Haemolytic anaemia Agranulocytosis Pancytopenia (life threatening) Bone marrow depression (life threatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (life threatening) (see section 4.4) Serum sickness like reaction	
Endocrine disorders					Syndrome of inappropriate secretion of antidiuretic hormone (SIADH)
Metabolism and Nutrition Disorders		Decreased appetite	Hyperglycaemia Hypoglycaemia (see section 4.4)		Hypoglycaemic coma (see section 4.4).
Psychiatric* Disorders		Psychomotor hyperactivity/ agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4) Hallucinations	Psychotic reactions (potentially culminating in suicidal ideations/thoughts or suicide attempts and completed suicide) (see section 4.4)	Mania Hypomania.
Nervous System Disorders*		Headache Dizziness, Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia, Tremor Seizures (including status epilepticus) (see section 4.4), Vertigo.	Migraine Disturbed coordination Gait disturbance Olfactory nerve disorders Intracranial hypertension and pseudotumor cerebri	Peripheral neuropathy and poly-neuropathy (see section 4.4).
Eye Disorders*			Visual disturbances (e. g. diploia)	Visual colour distortions.	
Ear and Labyrinth Disorders*			Tinnitus Hearing loss/Hearing impaired		
Cardiac Disorders**			Tachycardia		Ventricular arrhythmia and

					torsades de pointes (reported predominantly in patients with risk factors for QT prolongation), ECG QT prolonged (see sections 4.4 and 4.9)
Vascular Disorders**			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence	Antibiotic associated diarrhea incl. pseudomembraneous colitis.	Pancreatitis.	
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Cholestatic icterus Hepatitis	Liver necrosis (very rarely progressing to life-threatening hepatic failure) (see section 4.4)	
Skin and Subcutaneous Tissue Disorders		Musculoskeletal pain (e. g. extremity pain, back pain, chest pain) Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) (see section 4.4) Exacerbation of symptoms of myasthenia gravis (see section 4.4)	
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria (see section 4.4) Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions*		Asthenia Fever	Oedema Sweating (hyperhidrosis)		
Investigations		Increase in blood alkaline phosphatase	Increased amylase		International normalised ratio increased (in patients treated with Vitamin K antagonists)

* Very rare cases of prolonged (up to months or years), disabling and potentially irreversible serious drug reactions affecting several, sometimes multiple, system organ classes and senses (including reactions such as tendonitis, 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 quinolones and fluoroquinolones in some cases irrespective of pre-existing risk factors (see Section 4.4).

** Cases of aortic aneurysm and dissection, sometimes complicated by rupture (including fatal ones), and of regurgitation/incompetence of any of the heart valves have been reported in patients receiving fluoroquinolones (see section 4.4).

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 (see section 4.4).

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the recommended channels.

4.9 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, e. g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function, including urinary pH and acidify, if required, to prevent crystalluria. Patient should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of ciprofloxacin in overdoses.

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.

5.0 Pharmacological Properties

5.1 Pharmacodynamic Properties.

Pharmacotherapeutic group: Fluoroquinolones, **ATC code:** J01 MA 02.

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.

Pharmacokinetic/pharmacodynamic 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 physicochemical 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:

EUCAST Recommendations:

Microorganisms	Susceptible	Resistant
Enterobacteriaceae	S ≤ 0,5 mg/l	R > 1 mg/l
<i>Pseudomonas</i> spp.	S ≤ 0,5 mg/l	R > 1 mg/l
<i>Acinetobacter</i> spp.	S ≤ 1 mg/l	R > 1 mg/l
<i>Staphylococcus</i> spp.1	S ≤ 1 mg/l	R > 1 mg/l
<i>Haemophilus influenzae</i> und <i>Moraxella catarrhalis</i>	S ≤ 0,5 mg/l	R > 0,5 mg/l
<i>Neisseria gonorrhoeae</i>	S ≤ 0,03 mg/l	R > 0,06 mg/l
<i>Neisseria meningitidis</i>	S ≤ 0,03 mg/l	R > 0,06 mg/l
Non-species-related breakpoints*	S ≤ 0,5 mg/l	R > 1 mg/l

1 *Staphylococcus* spp.- breakpoints for ciprofloxacin relate to high dose therapy.

* Non-species-related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on 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 section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
<u>Aerobic Gram-positive micro-organisms</u> Bacillus anthracis (1)
<u>Aerobic Gram-negative micro-organisms</u> 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
<u>Anaerobic micro-organisms</u> Mobiluncus
<u>Other micro-organisms</u> Chlamydia trachomatis (\$) Chlamydia pneumoniae (\$) Mycoplasma hominis (\$) Mycoplasma pneumoniae (\$)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
<u>Aerobic Gram-positive micro-organisms</u> Enterococcus faecalis (\$) Staphylococcus spp. *(2)
<u>Aerobic Gram-negative micro-organisms</u> 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*
<u>Anaerobic micro-organisms</u> Peptostreptococcus spp. Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
<u>Aerobic Gram-positive micro-organisms</u> Actinomyces Enterococcus faecium Listeria monocytogenes
<u>Aerobic Gram-positive micro-organisms</u> Actinomyces Enterococcus faecium Listeria monocytogenes
<u>Aerobic Gram-negative micro-organisms</u> Stenotrophomonas maltophilia

<u>Anaerobic micro-organisms</u> Excepted as listed above
<u>Other micro-organisms</u> Mycoplasma genitalium Ureaplasma urealyticum
* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications + Resistance rate $\geq 50\%$ in one or more EU countries (S): 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, 500 mg 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.

5.2 Pharmacokinetic Properties

Absorption:

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg 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 100-750 mg produced dose-dependent maximum serum concentrations (C_{max}) between 0.56 and 3.7 mg/L. Serum concentrations increase proportionately with doses up to 1000 mg.

The absolute bioavailability is approximately 70-80%.

A 500 mg oral dose given every 12 hours has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to that produced by an intravenous infusion of 400 mg ciprofloxacin given over 60 minutes every 12 hours.

Distribution:

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.

Biotransformation:

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (M 1), sulphociprofloxacin (M 2), oxociprofloxacin (M 3) and formylciprofloxacin (M 4). 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	Feaces
Ciprofloxacin	44.7	25.0
Metabolites	11.30	7.5

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480-600 mL/kg/h. Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function leads to increased half-lives of ciprofloxacin of up to 12 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 (10 mg/kg three times daily) was observed.

In 10 children with severe sepsis C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L) after a 1-hour intravenous infusion of 10 mg/kg in children aged less than 1 year compared to 7.2 mg/L (range 4.7-11.8 mg/L) for children between 1 and 5 years of age. The AUC values were 17.4 mg*h/L (range 11.8-32.0 mg*h/L) and 16.5 mg*h/L (range 11.0-23.8 mg*h/L) in the respective age groups.

These values are within the range reported for adults at therapeutic doses. Based on population pharmacokinetic analysis of paediatric patients with various infections, the predicted mean half-life in children is approx. 4-5 hours and the bioavailability of the oral suspension ranges from 50 to 80%.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of single dose toxicity, repeated dose toxicity, carcinogenic potential, or toxicity to reproduction.

Like a number of other quinolones, ciprofloxacin is phototoxic in animals at clinically relevant exposure levels. Data on photomutagenicity/photocarcinogenicity show a weak photomutagenic or phototumorigenic effect of ciprofloxacin in-vitro and in animal experiments. This effect was comparable to that of other gyrase inhibitors.

Articular tolerability

As reported for other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints in immature animals. The extent of the cartilage damage varies according to age, species and dose; the damage can be reduced by taking the weight off the joints. Studies with mature animals (rat, dog) revealed no evidence of cartilage lesions. In a study in young beagle dogs, ciprofloxacin caused severe articular changes at therapeutic doses after two weeks of treatment, which were still observed after 5 months.

6. Pharmaceutical Particulars

6.1 List of excipients

- White Corn Starch.
- Sodium Starch Glycolate.
- Povidone K-30.
- Purified Water.
- Magnesium Stearate.
- Croscarmellose Sodium.
- Sodium Lauryl Sulphate.
- Aerosil 200 Pharma.
- Hydroxypropyl Methylcellulose 5CPS.
- Polyethylene Glycol 6000.
- Titanium Dioxide.
- Purified Talc.
- Isopropyl Alcohol.
- Monopropylene Glycol.
- Methylene Chloride.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

36 months (3 years) from the date of manufacture.

6.4 Special precautions for storage

Store in a dry place, below 30°C. Protect from light. Keep all medicines out of reach of children.

6.5 Nature and contents of container

Alu/PVC blister packs of 10 x 10's in a unit box along with literature insert.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7 Distribution Category

Prescription Only Medicine (POM).

7. Marketing authorization holder/Registrant.

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8. Manufacturer

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9. Marketing Authorisation Number(s)

Registration No(s): Kenya: H2003/167.

Malawi: PMPB/PL108/48.

Date of registration: Kenya: 2nd January 2003.

Retention: Retained annually.

10. Date of revision of the text:

March 2024.

11. Dosimetry (If Applicable):

Not Applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE):

Not Applicable.