

Cipro-250 Sandoz Film-Coated Tablets 250mg
Cipro-500 Sandoz Film-Coated Tablets 500mg**1. NAME OF THE MEDICINAL PRODUCT**

Cipro-250 Sandoz Film-coated Tablets 250mg

Cipro-500 Sandoz Film-coated Tablets 500mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION250 mg

Each film coated tablet contains 250 mg ciprofloxacin (as hydrochloride monohydrate).

500 mg

Each film coated tablet contains 500 mg ciprofloxacin (as hydrochloride monohydrate).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Appearance of the tablets

250 mg: white, round, scored on one side, embossment “cip 250”.

500 mg: white, oblong, scored on both sides, embossment “cip 500”.

4. CLINICAL PARTICULARS**4.1 Therapeutic indications**

- Uncomplicated and complicated infections caused by ciprofloxacin sensitive pathogens.
- Infections of the respiratory tract:
Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *E. coli*, *Pseudomonas*, *Haemophilus* spp., *Moraxella Catarrhalis*, *Legionella* spp. 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* or by *Staphylococcus*.
- Infections of the eyes
- Infections of the kidneys and/or the efferent urinary tract
- Infections of the genital organs, including adnexitis, gonorrhoea, prostatitis
- Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)
- Infections of the skin and soft tissue
- Infections of the bones and joints
- Sepsis
- Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)
- Selective intestinal decontamination in immunosuppressed patients

Consideration should be given to available official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration**Dosage regimen**

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

Adults

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Table 1: Recommended daily doses of ciprofloxacin oral in adults

Indications	Film-coated tablets (as mg ciprofloxacin)
Respiratory tract infection (according to severity and organism)	250-500 mg twice daily
Urinary tract infections: – acute, uncomplicated – cystitis in women (before menopause) – complicated	125 mg twice daily to 250 mg once or twice daily single dose 250 mg 250-500 mg twice daily
Gonorrhoea – extragenital – acute, uncomplicated	125 mg twice daily single dose 250 mg
Diarrhea	500 mg once or twice daily
Other infections (see indications)	500 mg twice daily
Particularly severe, life-threatening infections, i.e. -Streptococcal pneumonia – Recurrent infections in cystic fibrosis – Bone and joint infections – Septicemia – Peritonitis In particular when <i>Pseudomonas</i> , <i>Staphylococcus</i> or <i>Streptococcus</i> is present	750 mg twice daily

Missed dose

If a dose is missed, it should be taken as soon as the patient remembers and then treatment should be continued as prescribed. Double doses should not be taken to compensate for a missed dose.

Additional information on special patient populations

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 (see also '*Patients with renal and hepatic impairment*').

Children: contraindicated

Patients with renal and hepatic impairment

Adults

Patients with renal impairment

Table 2: Recommended doses for patients with renal impairment

Creatinine Clearance [mL/min/1.73 m²]	Serum Creatinine [mg/100 mL]	Total daily oral dose of ciprofloxacin
30 to 60	1.4 to 1.9	maximum 1000 mg
below 30	≥ 2.0	maximum 500 mg

Patients with renal impairment on hemodialysis

For patients with creatinine clearance between 30 and 60 mL/min/1.73m² (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 mL, the maximum daily dose of ciprofloxacin should be 1000 mg for oral administration.

For patients with creatinine clearance less than 30 mL/min/1.73m² (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 mL, the maximum daily dose of

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ciprofloxacin should be 500 mg for oral administration.

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD)

The maximum daily oral dose of ciprofloxacin should be 500 mg.

Patients with hepatic impairment

In patients with hepatic impairment, no dose adjustment is required.

Patients with renal and hepatic impairment

For patients with creatinine clearance between 30 and 60 ml/min/1.73m² (moderate renal impairment) or serum creatinine concentration between 1.4 and 1.9 mg/100 ml, the maximum daily oral dose of ciprofloxacin should be 1000 mg.

For patients with creatinine clearance less than 30 ml/min/1.73m² (severe renal impairment) or serum creatinine concentration equal or higher than 2.0 mg/100 ml, the maximum daily oral dose of ciprofloxacin should be 500 mg.

Method of administration

For oral use.

Tablets are to be swallowed whole with a small amount of fluid.

They can be taken independent of mealtimes.

If the tablets are taken on an empty stomach, the active substance is absorbed more rapidly.

In this case, ciprofloxacin tablets should not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) (see section 4.5).

If the patient is unable to take the ciprofloxacin tablets because of the severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration, the treatment can be continued orally.

Duration of treatment

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course. It is essential to continue therapy for at least 3 days after disappearance of the fever or of the clinical symptoms.

- Mean duration of treatment: 1 day for acute uncomplicated gonorrhoea 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 defences
- a maximum of 2 months in osteomyelitis
- and 7-14 days in all other infections

In streptococcal infections, the treatment must last at least 10 days because of the risk of late complications.

Infections caused by *Chlamydia* spp. should also be treated for a minimum of 10 days.

4.3 Contraindications

Hypersensitivity to the active substance, to other quinolones or to any of the excipients (see section 6.1).

Concomitant administration of ciprofloxacin and tizanidine (see section 4.5).

Ciprofloxacin must not be prescribed for children, adolescents, since there is no experience on the

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drug's safety in these patient groups and since, on the basis of animal studies, it is not entirely improbable that the drug could cause damage to articular cartilage in the immature organism.

4.4 Special warnings and precautions for use**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 agents.

***Streptococcus pneumoniae* infections**

Ciprofloxacin is not recommended for the treatment of pneumococcal infections due to limited efficacy against *Streptococcus pneumoniae*.

Genital tract infections

Epididymo-orchitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae* isolates. In genital tract infections thought or known to be due to *N. gonorrhoeae*, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing. Ciprofloxacin should be co-administered with another appropriate antibacterial agent unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. If clinical improvement is not achieved after 3 days of treatment, the therapy should be reconsidered.

Cardiac disorders

Ciprofloxacin is associated with cases of QT prolongation (see section 4.8). 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) (see section 4.5) 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).

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 (see section 4.5).

Gastrointestinal system

In the event of severe and persistent diarrhoea during or after treatment, a doctor must be consulted since this symptom can hide a serious intestinal disease (life-threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment (see section 4.8). In such cases, ciprofloxacin must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 250 mg four times a day). Medicinal products that inhibit peristalsis are contraindicated in this situation.

Renal and urinary system

Crystalluria related to the use of ciprofloxacin has been reported (see section 4.8). Patients receiving

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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 (see section 4.8). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage (see section 4.8).

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*.

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 (see section 4.8). If seizures occur, ciprofloxacin should be discontinued.

Psychiatric adverse reactions

Fluoroquinolones, including ciprofloxacin, have been associated with an increased risk of psychiatric adverse reactions, including: toxic psychosis, hallucinations, or paranoia; depression or suicidal thoughts or acts; anxiety, agitation, or nervousness; confusion, delirium, disorientation, or disturbances in attention; insomnia or nightmares; memory impairment. These adverse reactions may occur following the first dose. If these reactions occur in patients receiving ciprofloxacin, discontinue ciprofloxacin immediately and institute appropriate measures.

Peripheral neuropathy

Cases of sensory or sensorimotor axonal polyneuropathy affecting small and/or large axons resulting in paresthesias, hypoesthesias, dysesthesias and weakness have been reported in patients receiving fluoroquinolones including ciprofloxacin. Symptoms may occur soon after initiation of ciprofloxacin and may be irreversible. Ciprofloxacin should be discontinued immediately if the patient experiences symptoms of peripheral neuropathy including pain, burning, tingling, numbness, and/or weakness develop or other alterations of sensation including light touch, pain, temperature, position sense, and vibratory sensation.

Hypersensitivity

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In some instances, hypersensitivity and allergic reactions may occur following a single dose (see section 4.8), 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 (see section 4.8). In these cases, ciprofloxacin has to be discontinued and medical treatment (e.g. treatment for shock) is required.

Disabling and potentially irreversible serious adverse reactions

Fluoroquinolones, including ciprofloxacin, have been associated with disabling and potentially irreversible serious adverse reactions from different body systems that can occur together in the same patient. Commonly seen adverse reactions include tendinitis, tendon rupture, arthralgia, myalgia, peripheral neuropathy, and central nervous system effects (hallucinations, anxiety, depression, insomnia, severe headaches, and confusion). Patients of any age or without pre-existing risk factors have experienced these adverse reactions.

Discontinue ciprofloxacin immediately at the first signs or symptoms of any serious adverse reaction. In addition, avoid the use of fluoroquinolones, including ciprofloxacin, in patients who have experienced any of these serious adverse reactions associated with fluoroquinolones.

Myasthenia gravis

Ciprofloxacin should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated. Ciprofloxacin should be used with caution in patients with myasthenia gravis (see section 4.8).

Aortic aneurysm or 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

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of heart palpitations, or development of oedema of the abdomen or lower extremities.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Cases occurring up to several months after completion of therapy have been reported (see section 4.8). The risk of tendinopathy may be increased in elderly patients during strenuous physical activity, in patients treated concomitantly or previously treated with corticosteroids, in patients with renal impairment and patients with solid organ transplants.

At any sign of tendinitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment be discontinued. Ciprofloxacin should be used with caution in patients with a history of tendon disorders related to fluoroquinolone treatment.

Elderly patients, patients who are kidney, heart, and lung transplant recipients and patients on concomitant steroid therapy are at a higher risk of developing tendinitis and tendon rupture with fluoroquinolones use.

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 (see section 4.8).

Blood glucose disturbances

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. Severe cases of hypoglycaemia resulting in coma or death have been reported. In diabetic patients, careful monitoring of blood glucose is recommended. If a hypoglycaemic reaction occurs, discontinue ciprofloxacin and initiate appropriate therapy immediately.

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.

Vision disorders

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

4.5 Interaction with other medicinal products and other forms of interaction**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) (see section 4.4).

Chelation Complex Formation

The simultaneous administration of ciprofloxacin (oral) and multivalent cation-containing

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medicinal products and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminium, 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.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole containing medicinal products results in a slight reduction of C_{max} and AUC of ciprofloxacin.

Theophylline

Concurrent administration of ciprofloxacin and theophylline containing medicinal product can cause an undesirable increase in 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 concentrations should therefore be checked and the theophylline dose appropriately reduced (see 'Cytochrome P450' in section 4.4).

Other xanthine derivatives

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

NSAID

Animal studies have shown that the combination of very high doses of fluoroquinolones (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 necessary to control the serum creatinine concentrations in these patients frequently (twice a week).

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).

Probenecid

Probenecid interferes with renal secretion of ciprofloxacin. Co-administration of probenecid

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containing medicinal products and ciprofloxacin increases the ciprofloxacin serum concentrations.

Methotrexate

Renal tubular transport of methotrexate may be inhibited by concomitant administration of ciprofloxacin, potentially leading to increased plasma levels of methotrexate. This might increase the risk of methotrexate-associated toxic reactions. Therefore, patients under methotrexate therapy should be carefully monitored when concomitant ciprofloxacin therapy is indicated.

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.

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.

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 (see section 4.3).

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 (see 'Cytochrome P450' in section 4.4).

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 (see 'Cytochrome P450' in section 4.4).

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.

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Following concomitant administration of 250 mg ciprofloxacin with clozapine for 7 days, serum concentrations of clozapine and N-desmethylozapine 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 (see 'Cytochrome P450' in section 4.4).

Sildenafil

C_{max} and AUC of sildenafil were increased approximately two-fold 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 (see 'Cytochrome P450' in section 4.4).

Zolpidem

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

4.6 Pregnancy and lactation**Pregnancy**

The data that are available on administration of ciprofloxacin to pregnant women, indicate neither malformative nor fetoneonatal 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 foetal organism (see section 5.3), therefore, the use of ciprofloxacin is not recommended during pregnancy. Animal studies have not shown any evidence of teratogenic effects (malformations) (see section 5.3).

Lactation

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, the use of ciprofloxacin is not recommended to be used during breast-feeding (see section 5.3).

4.7 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 (see section 4.8). This applies particularly in combination with alcohol.

4.8 Undesirable effects

Adverse drug reactions (ADRs) based on all clinical studies with ciprofloxacin (oral, parenteral) sorted by CIOMS III categories of frequency are listed below (overall n = 51,621).

The frequencies of ADRs reported with ciprofloxacin are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Frequencies are defined as:

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very common ($\geq 1/10$),
common ($\geq 1/100$ to $< 1/10$),
uncommon ($\geq 1/1,000$ to $< 1/100$),
rare ($\geq 1/10,000$ to $< 1/1,000$),
very rare ($< 1/10,000$).

The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis (very rarely with possible fatal outcome)		
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytemia	Haemolytic anaemia Agranulocytosis Pancytopenia (life-threatening) Bone marrow depression (life-threatening)	
Immune System Disorders			Allergic reaction Allergic edema / angioedema	Anaphylactic reaction Anaphylactic shock (life-threatening) Serum sickness-like reaction	
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycemia Hypoglycemia		
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide)	
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including	Migraine Disturbed coordination Smell disorders Hyperesthesia	Peripheral neuropathy (that may be irreversible) and

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			status epilepticus) Vertigo	Intracranial hypertension (pseudotumor cerebri)	polyneuro- pathy
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss	Hearing impaired	
Cardiac Disorders			Tachycardia		QT prolonga- tion, ventricular arrhythmia, torsades de pointes*
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis	
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 minor Erythema nodosum Stevens-Johnson syndrome (potentially life- threatening) Toxic epidermal necrolysis (potentially life- threatening)	Acute generalised exanthema- tous pustulosis (AGEP)

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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 Haematuria Crystalluria Tubulointerstitial nephritis		
General Disorders and Administration Site Conditions		Unspecific pain Feeling unwell Fever	Edema Sweating (hyperhidrosis)	Gait disturbance	
Investigations		Increase in blood alkaline phosphatase	Abnormal Prothrombin level Increased amylase		International normalised ratio (INR) increased (in patients treated with Vitamin K antagonists)

*These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

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 disturbance of senses.

Keep the doctor informed of any undesired effects which occur during the use of this medication.

4.9 Overdose

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 crystalluria. 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 haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones,
ATC code: J01MA02

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibacterial agent.

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Mechanism of action

Ciprofloxacin has *in vitro* activity against a wide range of Gram-negative and Gram-positive organisms. The bactericidal action of ciprofloxacin results from inhibition of bacterial type II topoisomerases (DNA-gyrase) and topoisomerase IV, which are required for bacterial DNA replication, transcription, repair and recombination.

Mechanism of resistance

In vitro resistance to ciprofloxacin is commonly due to target site mutations in topoisomerase IV and DNA gyrase through multiple-step mutations. Single mutations may result in reduced susceptibility rather than clinical resistance, but multiple mutations generally result in clinical resistance to ciprofloxacin and cross-resistance across the fluoroquinolone class.

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 the *qnr* gene has been reported. Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides, and tetracyclines may not interfere with the antibacterial activity of ciprofloxacin. Organisms resistant to these drugs may be susceptible to ciprofloxacin.

The minimal bactericidal concentration (MBC) generally does not exceed the minimal inhibitory concentration (MIC) by more than a factor of 2.

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 utility of the agent, in at least some types of infections is questionable.

The bacterial genus and species listed below have been shown to commonly be susceptible to ciprofloxacin *in vitro*:

Aerobic Gram-positive Microorganisms

Bacillus anthracis
Staphylococcus aureus (methicillin-susceptible isolates)
Staphylococcus saprophyticus
Streptococcus spp.

Aerobic Gram-negative Microorganisms

<i>Aeromonas spp.</i>	<i>Moraxella catarrhalis</i>
<i>Brucella spp.</i>	<i>Neisseria meningitidis</i>
<i>Citrobacter koseri</i>	<i>Pasteurella spp.</i>
<i>Francisella tularensis</i>	<i>Salmonella spp.*</i>
<i>Haemophilus ducreyi</i>	<i>Shigella spp.</i>
<i>Haemophilus influenzae</i>	<i>Vibrio spp.</i>
<i>Legionella spp.</i>	<i>Yersinia pestis</i>

Anaerobic Microorganisms

Mobiluncus

Cipro-250 Sandoz Film-Coated Tablets 250mg
Cipro-500 Sandoz Film-Coated Tablets 500mg**Other Microorganisms**

Chlamydia trachomatis
Chlamydia pneumoniae
Mycoplasma hominis
Mycoplasma pneumoniae

The following microorganisms show varying degrees of susceptibility to ciprofloxacin: *Acinetobacter baumannii*, *Burkholderia cepacia*, *Campylobacter* spp., *Citrobacter freundii*, *Enterococcus faecalis*, *Enterobacter aerogenes*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, *Morganella morganii*, *Neisseria gonorrhoeae*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia* spp., *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Serratia marcescens*, , *Peptostreptococcus* spp., *Propionibacterium acnes*.

The following microorganisms are considered inherently resistant to ciprofloxacin: *Staphylococcus aureus* (methicillin-resistant) and *Stenotrophomonas maltophilia*, *Actinomyces*, *Enterococcus faecium*, *Listeria monocytogenes*, *Mycoplasma genitalium*, *Ureaplasma urealyticum*, Anaerobic microorganisms (Except *Mobiluncus*, *Peptostreptococcus*, *Propionibacterium acnes*).

5.2 Pharmacokinetic properties**Absorption**

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of ciprofloxacin film-coated tablets, ciprofloxacin is absorbed rapidly and extensively, mainly from the small intestine, reaching maximum serum concentrations 1-2 hours later. The absolute bioavailability is approximately 70 – 80%. Maximum serum concentrations (C_{max}) and total areas under serum concentration vs. time curves (AUC) increased in proportion to dose up to doses of 1000 mg administered orally.

Distribution

The protein binding of ciprofloxacin is low (20-30%), and the substance is present in plasma largely in a non-ionized form. Ciprofloxacin can diffuse freely into the extravascular space. The large steady-state distribution volume of 2-3 L/kg body weight shows that ciprofloxacin penetrates in tissues resulting in concentrations which clearly exceed the corresponding serum levels.

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.

Elimination

Ciprofloxacin is largely excreted unchanged both renally and, to a smaller extent, faecally. 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.

Cipro-250 Sandoz Film-Coated Tablets 250mg
Cipro-500 Sandoz Film-Coated Tablets 500mg**5.3 Preclinical safety data****Acute toxicity**

The acute toxicity of ciprofloxacin after oral administration can be classified as very low. Depending on the individual species, the LD₅₀ after intravenous infusion is 125 – 290 mg/kg.

Chronic Tolerability Studies over 6 monthsOral administration

Doses up to and including 500 mg/kg and 30 mg/kg were tolerated without damage by rats and monkeys, respectively. Changes in the distal renal tubules were again observed in some monkeys in the highest-dose group (90 mg/kg).

Carcinogenicity

In carcinogenicity studies in mice (21 months) and rats (24 months) with doses up to approximately 1000 mg/kg body weight/day in mice and 125 mg/kg body weight/day in rats (increased to 250 mg/kg body weight /day after 22 weeks), there was no evidence of a carcinogenic potential at any dose level.

Reproduction ToxicologyFertility Studies in Rats

Fertility, the intrauterine and postnatal development of the young, and the fertility of F1 generation were not affected by ciprofloxacin.

Embryotoxicity Studies

These yielded no evidence of any embryotoxic or teratogenic action of ciprofloxacin.

Perinatal and Postnatal Development in Rats

No effects on the perinatal or postnatal development of the animals were detected. At the end of the rearing period histological investigations did not show any sign of articular damage in the young.

Mutagenicity

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin.

Although two of the eight *in vitro* assays (i.e. the Mouse Lymphoma Cell Forward Mutation Assay and the Rat Hepatocyte Primary Culture DNA Repair Assay [UDS]) were positive, all of the *in vivo* test systems covering all relevant endpoints gave negative results.

Articular Tolerability Studies

As it is also known 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 at high doses (1.3 to 3.5 times the therapeutic dose) caused articular changes after two weeks of treatment, which were still observed after 5 months. At therapeutic doses no effects were observed.

6. PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Core: cellulose, microcrystalline; sodium starch glycolate (type A); povidone; silica, colloidal anhydrous; stearic acid; magnesium stearate; croscarmellose, sodium

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Film: hypromellose; macrogol 6000; talc; titanium dioxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Refer to outer carton.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container**Ciprofloxacin 250 mg Film-Coated Tablets**

6, 10, 12, 14, 20, 28 and 100 film-coated tablets in PVC/aluminium or PP/aluminium blisters.

Ciprofloxacin 500 mg Film-Coated Tablets

10, 12, 14, 16, 20, 28, 50 (10 x 5) and 100 film-coated tablets in PVC/aluminium or PP/aluminium blisters containing 20, 30, 100, 120 and 160 film-coated tablets.

Not all pack sizes or pack types may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. PRODUCT REGISTRATION HOLDER

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8. DATE OF REVISION OF THE TEXT

Nov 2020