Name of the medicinal product

Ciprobay 250mg film-coated tablets
Ciprobay 500mg film-coated tablets
Ciprobay 100 Infusion Solution 100 mg/50 ml
Ciprobay 200 Infusion Solution 200 mg/100 ml

Qualitative and Quantitative Composition

250mg
Each film-coated tablet contains 250 mg ciprofloxacin as hydrochloride.

500mg
Each film-coated tablet contains 500 mg ciprofloxacin as hydrochloride.

100 mg/50 ml
Each glass bottle with 50 ml solution for infusion contains 100 mg ciprofloxacin. The sodium content is 177 mg (7.7 mmol).

200 mg/100 ml
Each glass bottle with 100 ml solution for infusion contains 200 mg ciprofloxacin. The sodium content is 354 mg (15.4 mmol).

Pharmaceutical form

250mg
Round, nearly white to slightly yellowish film-coated tablets marked with “CIP score 250” on one side and a “Bayer cross” on the reverse side. The tablet can be divided into equal halves.

500mg
Oblong, nearly white to slightly yellowish film-coated tablets marked with “CIP score 500” on one side and “BAYER” on the reverse side. The tablet can be divided into equal halves.

100 mg/50 ml
Clear, nearly colourless to slightly yellowish solution. The pH-value of the solution for infusion ranges from 3.9 to 4.5.

200 mg/100 ml
Clear, nearly colourless to slightly yellowish solution. The pH-value of the solution for infusion ranges from 3.9 to 4.5.

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.

Dosage and method of administration

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

Adults

Table 1: Recommended daily doses of Ciprobay oral and intraveneous in adults

Indications	Film-coated tablets (as mg ciprofloxacin)	Solution for infusion (as mg ciprofloxacin)
Respiratory tract infection (according to severity and organism)	250-500 mg twice daily	200-400 mg twice daily
Urinary tract infections: -acute, uncomplicated	125 mg twice daily to 250 mg once or twice daily	100 mg twice daily
-cystitis in women (before menopause)	single dose 250 mg	single dose 100 mg
-complicated	250-500 mg twice daily	200 mg twice daily
Gonorrhoea -extragenital	125 mg twice daily	100 mg twice daily
-acute, uncomplicated	single dose 250 mg	single dose 100 mg
Diarrhea	500 mg once or twice daily	200 mg twice daily
Other infections (see indications)	500 mg twice daily	200-400 mg twice daily
Particularly severe, life-threatening infections, i.e. -Streptococcal pneumonia -Recurrent infections in cystic fibrosis -Bone and joint infections	750 mg twice daily	400 mg three times daily

-Septicemia -Peritonitis In particular when *Pseudomonas*, *Staphylococcus* or *Streptococcus* is present		

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 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 3: Recommended doses for patients with renal impairment

Creatinine Clearance [mL/min/1.73 m^2]	**Serum Creatinine [mg/100 mL]**	**Total daily oral dose of ciprofloxacin**	**Total daily intravenous dose of ciprofloxacin**
30 to 60	1.4 to 1.9	maximum 1000 mg	maximum 800 mg
below 30	≥ 2.0	maximum 500 mg	maximum 400 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 or 800. mg for an intravenous regimen.
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 ciprofloxacin should be 500 mg for oral administration or 400 mg for an intravenous regimen on dialysis days after dialysis.

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

Addition of Ciprobay solution for infusion to the dialysate (intraperitoneal): 50 mg ciprofloxacin / liter dialysate administered 4 times a day every 6 hours.
The maximum daily oral dose of ciprofloxacin should be 500 mg (1 x 500 mg Ciprobay film-coated tablet or 2 x 250 mg Ciprobay film-coated tablets).

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 or 800 mg for an intravenous regimen.
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 or 400 mg for an intravenous regimen.

Method of administration

For oral Use

Ciprobay film-coated 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, the Ciprobay film-coated tablets should not be taken concurrently with dairy products or with mineral- fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice) (see *'Interaction with other medicinal products and other forms of interaction'*).

If the patient is unable to take the Ciprobay film-coated 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.

Intravenous Infusion

Ciprobay solution for infusion should be administered by intravenous infusion. In adult patients, infusion time is 60 minutes for 400 mg Ciprobay infusion solution and 30 minutes for 200 mg Ciprobay infusion solution. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The solution for infusion can be infused either directly or after mixing with other compatible solutions for infusions.

<u>Incompatibilities</u>

Ciprofloxacin solution for infusion is compatible with physiological saline, Ringer solution and Ringer lactate solution, 5 % and 10 % glucose solutions, 10 % fructose solution, and 5 % glucose solution with 0.225 % NaCl or 0.45 % NaCl. When ciprofloxacin solution for infusion are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.

Unless compatibility with other solutions for infusion/medicinal products has been confirmed, the infusion solution must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discolouration.

Incompatibility appears with all infusion solutions/medicinal products that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially in

combination with solutions adjusted to an alkaline pH (pH of the ciprofloxacin solution for infusion: 3.9-4.5).

Only clear solutions are to be used.

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.

Contraindications

Hypersensitivity to ciprofloxacin or other quinolone or any of the excipients (see ’List of excipients’).

Concurrent administration of ciprofloxacin and tizanidine (see, ’Interaction with other medicinal products and other forms of interaction’).

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

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, Ciprobay should be used in combination with an appropriate antibacterial agent.

Streptococcus pneumoniae infections

Ciprobay is not recommended for 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

Ciprobay is associated with cases of QT prolongation (see 'Undesirable effects'). 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 Ciprobay with concomitant drugs that can result in prolongation with the QT interval (e.g., class IA or III antiarrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see 'Interaction with other medicinal products and other forms of interaction') 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 'Interaction with other medicinal products and other forms of interaction').

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 'Undesirable effects'). In such cases, Ciprobay 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 "Undesirable effects"). Patients receiving ciprofloxacin should be well hydrated and excessive alkalinity of the urine should be avoided.

Hepatobiliary system

Cases of hepatic necrosis and life-threatening hepatic failure have been reported with Ciprobay. 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 'Undesirable effects'). There can be temporary increase in transaminases, alkaline phosphatase, or cholestatic jaundice, especially in patients with previous liver damage (see 'Undesirable effects')

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

Ciprobay, 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), Ciprobay 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 'Undesirable effects'). If seizures occur, Ciprobay should be discontinued.

Psychiatric adverse reactions

Fluoroquinolones, including Ciprobay, 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 Ciprobay, discontinue Ciprobay 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 Ciprobay. Symptoms may occur soon after initiation of Ciprobay and may be irreversible. Ciprobay 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

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

Disabling and potentially irreversible serious adverse reactions

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

Myasthenia gravis

Ciprobay should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated. Ciprobay should be used with caution in patients with myasthenia gravis (see 'Undesirable effects').

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 a 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, Behçet´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.

Tendinitis and tendon rupture

Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with Ciprobay, even within the first 48 hours of treatment Cases occurring up to several months after completion of therapy have been reported (see 'Undesirable effects'). 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. Ciprobay 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 Ciprobay should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitization (i.e. sunburn-like skin reactions) occurs (see 'Undesirable effects').

Blood glucose disturbances

As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycemia and hyperglycemia have been reported with Ciprobay. In Ciprobay-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 Ciprobay and initiate appropriate therapy immediately.

Injection site reaction (applicable to Solution for Infusion)

Local intraveneous site reactions have been reported with the intravenous administration of Ciprobay (see 'Undesirable effects'). These reactions are more frequent if the infusion time is 30 minutes or less. These may appear as local skin reactions which resolve rapidly upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

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 Ciprobay.

Sodium load for Ciprobay Solution for infusion with 0.9% NaCl

In patients for whom sodium intake is of medical concern (patients with congestive heart failure, renal failure, nephrotic syndrome, etc.), the additional sodium load should be taken into account.

Vision disorders

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

Interaction with other medicinal products and other forms of interaction

Drugs known to prolong QT interval

Ciprobay, 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 'Special warnings and precautions for use').

Chelation Complex Formation
The simultaneous administration of Ciprobay (oral) and multivalent cation-containing 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, Ciprobay 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 H_2 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 Ciprobay 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 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 (see 'Cytochrome P450' in section -'Special warnings and precautions for use'*)*.

Other xanthine derivatives
On concurrent administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline) containing products, 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 Ciprobay 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 ciprobay with a vitamin K antagonist (e.g., warfarin, acenocoumarol, phenprocoumon, or fluindione).

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

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciprobay, 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 Ciprobay therapy is indicated.

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

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 'Special warnings and precautions for use').

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

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 concentration 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 Ciprobay are advised (see 'Cytochrome P450' in section 'Special warnings and precautions for use').

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 Ciprobay 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 *'Special warnings and precautions for use'*).

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

Pregnancy and lactation

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 of animal studies it cannot be excluded that the drug could cause damage to articular cartilage in the immature foetal organism (see 'Preclinical safety data'), therefore, the use of Ciprobay is not recommended during pregnancy. Animal studies have not shown any evidence of teratogenic effects (malformations) (see 'Preclinical safety data').

Lactation
Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, the use of Ciprobay -is not recommended to be used during breast-feeding (see 'Preclinical safety data).

Effects on ability to drive or 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 'Undesirable effects'). This applies particularly in combination with alcohol.

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 = 51621,).

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

Frequencies are defined as:
very common (≥ 1/10),
common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 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”.

Table 4: ADRs table

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 Anemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytemia	Hemolytic anemia 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		

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
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 behavior, 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 status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumor cerebri)	Peripheral neuropathy (that may be irreversible) and polyneuropathy
Eye Disorders			Visual disturbances	Visual colour distortions	
Ear and Labyrinth Disorders			Tinnitus Hearing loss	Hearing impaired	
Cardiac Disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de pointes *
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis	
Respiratory, Thoracic and Mediastinal Disorders			Dyspnea (including asthmatic condition)		
Gastrointestinal Disorders	Nausea Diarrhea	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)	

System Organ Class	Common	Uncommon	Rare	Very Rare	Not Known
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 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	Injection and infusion site reactions (only intravenous administration)	Unspecific pain Feeling unwell Fever	Edema 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 post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see 'Special warnings and precautions for use').

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.

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, Thrombocytemia, Confusion and disorientation, Hallucinations, Par- and dysesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Edema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

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

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.

Pharmacodynamic Properties

Pharmacotherapeutic group: Fluoroquinolones

ATC Code: J01MA02

Ciprofloxacin is a synthetic broad spectrum fluoroquinolone antibacterial agent.

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 where 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

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

Anaerobic Microorganisms

Mobiluncus

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 freudii, Enterococcus faecalis, Enterobacter aerogenes, Enterobacter clocae, 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, Enteroccus faecium, Listeria monocytogenes, Mycoplasma genitalium , Ureaplasma urealitycum, Anaerobic micro-organisms (Except *Mobiluncus, Peptostreptococus, Propionibacterium acnes*).

Pharmacokinetic Properties

Absorption

Film-coated tablets

Following oral administration of single doses of 250 mg, 500 mg, and 750 mg of Ciprobay 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.

Solution for Infusion

Following an intravenous infusion of ciprofloxacin the mean maximum serum concentrations were achieved at the end of infusion. Pharmacokinetics of ciprofloxacin were linear over the dose range up to 400 mg administered intravenously.

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.

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 LD_{50} after intravenous infusion is 125 – 290 mg/kg.

Chronic Tolerability Studies over 6 months

Oral 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).

Parenteral administration
In monkeys slightly elevated urea and creatinine concentrations and changes in the distal renal tubules were recorded in the highest-dose group (20 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 Toxicology
Fertility 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 five months. At therapeutic doses no effects were observed.

List of excipients

Ciprobay film-coated tablets
Tablet core:
Cellulose microcrystalline
Crospovidone
Maize starch
Magnesium stearate
Silica colloidal anhydrous

Film-coat:

Hypromellose
Macrogol 4000
Titanium dioxide (E171)

Ciprobay solution for infusion
Lactic acid 20%
Sodium chloride
Hydrochloric acid concentrated
Water for injections

Shelf life
Please refer to labels

Special precautions for storage and use
Do not store above 30˚C = 86˚F.

Ciprofloxacin solution for infusion
Protect from light. Do not refrigerate or freeze. At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature (15°C – 25°C). It is therefore recommended not to store the infusion solution in a refrigerator. The product should be inspected visually for particles prior to administration. Only clear solution free from particles should be used. For ease of use, the infusion vial stopper should be penetrated in the central ring. Penetration of the outer ring may result in damage to the vial stopper.

Keep drugs out of reach of children. Do not use after the expiry date.
Please read the package insert carefully. Ask your doctor for more information.

Pack Size

Ciprobay tablets: each pack contains 10 film-coated tablets.
Ciprobay Infusion Solution: 1 glass bottle per pack.

Not all strengths are marketed in all countries.

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If you would like to report a side effect for any Bayer Pharmaceutical or Consumer Health product, you can do it easily using our online reporting portal: https://safetrack-public.bayer.com/ or scan the QR code available below. Please also remember to seek medical advice directly from your doctor or pharmacist.

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