Ciprobay®

1. NAME OF THE MEDICINAL PRODUCT

Ciprobay 250 mg film-coated tablets
Ciprobay 500 mg film-coated tablets
Ciprobay 100 mg solution for infusion (0.9% NaCl)
Ciprobay 200 mg solution for infusion (0.9% NaCl)
Ciprobay 400 mg solution for infusion (0.9% NaCl)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION IN TERMS OF THE ACTIVE SUBSTANCE(S) Ciprobay film-coated tablets

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

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

Ciprobay solution for infusion (0.9% NaCl)

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)

400 mg/200 mL:
Each glass bottle with 200 mL solution for infusion contains 400 mg ciprofloxacin. The sodium content is 708 mg (30.8 mmol).

3. PHARMACEUTICAL FORM Film-coated tablets

250 mg
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.

500 mg
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.

Solution for infusion (0.9% NaCl) 100 mg/50 mL
Clear, nearly colorless 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 colorless to slightly yellowish solution.
The pH-value of the solution for infusion ranges from 3.9 to 4.5.

400 mg/200 mL
Clear, nearly colorless to slightly yellowish solution.
The pH-value of the solution for infusion ranges from 3.9 to 4.5.

4. CLINICAL PARTICULARS

4.1 Indication(s)

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

For Ciprobay film-coated tablets and solution for infusion:
Uncomplicated and complicated infections caused by ciprofloxacin susceptible pathogens.

*Infections of the respiratory tract:

Ciprofloxacin can be regarded as an advisable treatment for pneumonias caused by Klebsiella, Enterobacter, Proteus, E. coli, Pseudomonas, Haemophilus, Moraxella catarrhalis, Legionella and Staphylococcus.

*Infections of the middle ear (otitis media), of the paranasal sinuses (sinusitis), especially if these are caused by Gram-negative organisms including Pseudomonas aeruginosa or by staphylococci.

Infections of the eyes

*Infections of the kidneys and/or the efferent urinary tract

Infections of the genital organs, including adnexitis, gonorrhea, prostatitis and excluding vaginal infections
Infections of the abdominal cavity (e.g. infections of the gastrointestinal tract or of the biliary tract, peritonitis)

Infections of the skin and soft tissue

Infections of the bones and joints

*Sepsis

Infections or imminent risk of infection (prophylaxis) in patients whose immune system has been weakened (e.g. patients on immunosuppressants or have neutropenia)

*Ciprobay should be only used:

- When Pseudomonas is considered AND the patient is allergic to antipseudomonal penicillins/ cephalosporin; or
- For resistant organism with no other alternative antibiotics available.

For Ciprobay film-coated tablets only:
Prophylaxis of invasive infections due to Neisseria meningitidis.

Children and adolescents
Ciprofloxacin may be used in children for the second- and third-line treatment of complicated urinary tract infections and pyelonephritis due to Escherichia coli (age range applied in clinical studies: 1 – 17 years) and for the treatment of broncho-pulmonary infections of cystic fibrosis associated with Pseudomonas aeruginosa (age range applied in clinical studies: 5 – 17 years).

Treatment should only be initiated after careful benefit/risk evaluation, due to possible adverse events related to joints and/or surrounding tissues.

The clinical trials in children were performed in the indications listed above. For other indications clinical experience is limited.

Inhalational anthrax (post-exposure) in adults and in children (for Ciprobay filmcoated tablets only):
To reduce the incidence or progression of disease following exposure to aerosolized Bacillus anthracis.

4.2 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 in adults

Indications	Daily dose of ciprofloxacin in mg for Ciprobay filmcoated tablets	Daily dose of ciprosolution for for Ciprobay infusion
Infections of the respiratory tract I (according to severity and organism)	2 x 500 mg to 2 x 750mg	2 x 400 mg to 3 x 400 mg
Urinary tract infections: - acute, uncomplicated - cystitis in women (before menopause) - complicated	 2 x 250 mg to 2 x 500 mg single dose 500 mg 2 x 500 mg to 2 x 750 mg	 2 x 200 mg to 2 x 400 mg N/A 2 x 400 mg to 3 x 400 mg
Genital infections - uncomplicated gonorrhea (including extragenital sites of infection) - adnexitis, prostatitis, epididymo-orchitis	1 x 500 mg 2 x 500 mg to 2 x 750 mg	N/A 2 x 400 mg to 3 x 400 mg
Diarrhea	2 x 500 mg	2 x 400 mg
Other infections (see indications)	2 x 500 mg	2 x 400 mg
Particularly severe, lifethreatening infections, i.e. - Recurrent infections in cystic fibrosis - Bone and joint infections - Septicemia - Peritonitis. In particular when Pseudomonas, Staphylococcus or Streptococcus is present	2 x 750 mg	3 x 400 mg
Inhalational anthrax (post exposure)	2 x 500 mg	N/A

Prophylaxis of invasive infections due to Neisseria meningitides	1 x 500 mg as a single dose	N/A

Children and adolescents Table 2: Recommended daily doses of Ciprobay oral in children and adolescents

Indications	Daily dose of ciprofloxacin in mg for Ciprobay oral	Daily dose of ciprofloxacin in mg for Ciprobay intravenous
Infections in cystic fibrosis	2 × 20mg/kg body weight (maximum of 750 mg per dose)	3 × 10 mg/kg body weight (maximum of 400 mg per dose)
Complicated urinary tract	2 × 10mg/kg body weight	3 × 6 mg/kg body weight
infections and pyelonephritis	to 2 × 20mg/kg body weight (maximum of 750 mg per dose)	to 3 × 10 mg/kg body weight (maximum of 400 mg per dose)
Inhalational anthrax (postexposure)	2 × 15mg/kg body weight (maximum of 500mg per dose)	N/A

Missed dose
If a dose is missed, it should be taken as anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remain before the next dose, the missed dose should not be taken and treatment should be continued as prescribed with the next scheduled dose. Double doses should not be taken to compensate for a missed dose.

Additional information on special patient population

Children and adolescents

For recommended dosage regimen see Table 2.

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’)

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/100mL]	Total daily oral dose of ciprofloxacin	Total daily intravenous dose of ciprofloxacin
30 to 60	1.4 to 1.9	maximum 1000 mg	maximum 800mg
below 30	≥2.0	maximum 500mg	maximum 400mg

• Patients with renal impairment on hemodialysis

- For patients with creatinine clearance between 30 and 60 mL/min/1.73m^2 (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/1.73m^2 (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 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 (1 x 500 mg Ciprobay film-coated tablet or 2 x 250 mg Ciprobay film-coated tablets).

• Patients with hepatic impairment

- In patients with impaired hepatic function no dose adjustment is required

• Patients with renal and hepatic impairment

- For patients with creatinine clearance between 30 and 60 mL/min/1.73m^2 (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/1.73m^2 (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.

Children and adolescents

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

Inhalational Anthrax (Post-exposure) in Adults and Children

For recommended dosage regimen see Table 1 (for adults) and Table 2 (for children and adolescents), respectively.

Method of administration
Film-coated tablets
For oral use

Ciprobay film-coated tablets are to be swallowed whole with a small amount of fluid.

Ciprobay film-coated tablets can be taken independently of mealtimes.

If they are taken on an empty stomach, the active substance is absorbed more rapidly. In this case, 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 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.

Solution for infusion
For intravenous use
Ciprobay solution for infusion should be administered by intravenous infusion over a period of 60 minutes. 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 infusion.

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

Incompatibility appears with all solutions for infusion/medicinal products that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially on combination with solutions adjusted to an alkaline pH (pH of Ciprobay solutions 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

Adults

- 1 day for acute uncomplicated gonorrhea and cystitis
- up to 7 days for infections of the kidneys, urinary tract and abdominal cavity
- over the entire period of the neutropenic phase in patients with weakened body defenses
- a maximum of 2 months in osteomyelitis
- and 7 – 14 days in all other infections

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

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

Children and adolescents

- Cystic Fibrosis

For broncho-pulmonary infections of cystic fibrosis associated with Pseudomonas aeruginosa infection in pediatric patients (aged 5 – 17 years), the duration of treatment is 10 – 14 days.

- Complicated Urinary Tract Infections and Pyelonephritis

For complicated urinary tract infections or pyelonephritis due to Escherichia coli, the duration of treatment is 10 – 21 days.

Inhalational Anthrax (Post-exposure) in Adults and Children
60 days from the confirmation of Bacillus anthracis exposure

4.3 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’).

4.4 Special warnings and precautions for use

The use of Ciprobay should be avoided in patients who have experienced serious adverse reactions in the past when using fluoroquinolone containing products (see section Undesirable effects). Treatment of these patients with Ciprobay should only be initiated in the absence of alternative treatment options and after careful benefit/ risk assessment.

Severe infections and/or infections due to Gram-positive or anaerobic bacteria For the treatment of severe infections, staphylococcal infections and infections involving anaerobic bacteria, 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

Genital tract infections may be caused by fluoroquinolone-resistant Neisseria gonorrhoeae isolates. In genital tract infections thought or known to be due to Neisseria gonorrhoeae, it is particularly important to obtain local information on the prevalence of resistance to ciprofloxacin and to confirm susceptibility based on laboratory testing.

Cardiac disorders

Ciprobay is associated with cases of QT prolongation (see section '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).

Children and adolescents

As with medicinal products in its class, ciprofloxacin has been shown to cause arthropathy in weight-bearing joints of immature animals (see 'Undesirable effects'). The analysis of available safety data from Ciprobay use in patients less than 18 years of age, the majority of whom had cystic fibrosis, did not disclose any evidence of drug-related cartilage or articular damage. The use of ciprofloxacin for indications other than the treatment of broncho-pulmonary infections of cystic fibrosis caused by Pseudomonas aeruginosa infection (children aged 5 – 17 years), complicated urinary tract infections and pyelonephritis due to Escherichia coli (children aged 1 – 17 years), and for the use in inhalational anthrax (post-exposure) was not studied. For other indications clinical experience is limited.

Hypersensitivity

In some instances, hypersensitivity and allergic reactions may occur following a single dose (see 'Undesirable effects'), a physician should be informed immediately.

Anaphylactic/anaphylactoid reactions in very rare instances can progress to a lifethreatening 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.
Cases of acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction (Kounis syndrome) have also been reported (see 'Undesirable effects'). In the event of Kounis syndrome while on treatment with ciprofloxacin, discontinue Ciprobay immediately.

Gastrointestinal system
In the event of severe and persistent diarrhea during or after treatment, a physician must be consulted since this symptom can hide a serious intestinal disease (life-threatening pseudomembranous colitis with possible fatal outcome), requiring immediate treatment(see 'Undesirable effects'). In such cases, Ciprobay must be discontinued and appropriate therapy initiated (e.g. vancomycin, orally, 4 x 250 mg/day). Medicinal products that inhibit peristalsis are contraindicated in this situation.

Hepatobiliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with 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, who are treated with Ciprobay (see 'Undesirable effects').

Prolonged, disabling and potentially irreversible serious adverse drug reactions Very rare cases of prolonged (continuing months or years), disabling and potentially irreversible serious adverse reactions affecting different, sometimes multiple body systems (musculoskeletal, nervous, psychiatric and senses) have been reported in patients receiving fluoroquinolones irrespective of their age and pre-existing risk factors.
Ciprobay should be discontinued immediately at the first signs or symptoms of any serious adverse reaction and patients should be advised to contact their prescriber for advice.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (especially but not limited to Achilles tendon), sometimes bilateral, may occur as early as within 48 hours of starting treatment with fluoroquinolones and have been reported to occur even up to several months after discontinuation of treatment. The risk of tendinitis and tendon rupture is increased in older patients (above 60 years of age), with renal impairment, patients with solid organ transplants, and those treated concurrently with corticosteroids. Therefore, concomitant use of corticosteroids should be avoided.
At the first sign of tendinitis (e.g. painful swelling, inflammation) the treatment with Ciprobay 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.

Aortic aneurvsm and dissection

Epidemiologic studies report an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the older population. Therefore, fluoroquinolones should only be used after careful benefit-risk assessment and after consideration of other therapeutic options in patients with positive family history of aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

Exacerbation of myasthenia gravis

Ciprobay should be used with caution in patients with myasthenia gravis, because symptoms can be exacerbated.

Fluroquinolones have neuromuscular blocking activity and may exacerbate muscle weakeness in person with myasthenia gravis. Post-marketing serious adverse events, including deaths and requirement for ventilator support have been associated with fluroquionolones use in persons with myasthenia gravis. Avoid fluroquinolones in patients with known history of myasthenis gravis.

Seizures

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 reactions

Psychiatric reactions may occur even after the first administration of fluoroquinolones, including Ciprobay. In rare cases, depression or psychotic reactions can progress to suicidal ideations/thoughts and self-injurious behavior, such as attempted or completed suicide (see ‘Undesirable effects’). In the event that the patient develops these reactions, Ciprobay should be discontinued and appropriate measures instituted

Peripheral neuropathy

Cases of sensory or sensorimotor polyneuropathy resulting in paresthesias, hypoesthesias, dysesthesias, or weakness have been reported in patients receiving quinolones and

fluoroquinolones. Patients under treatment with Ciprobay should be advised to inform their doctor prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see 'Undesirable effects').

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').

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').

Dysglycemia

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. In diabetic patients, careful monitoring of blood glucose is recommended (see 'Undesirable effects').

Injection site reaction

Local intravenous 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.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs known to prolong QT interval

Ciprobay, like other fluroquinolones, should be used with caution in patients receiving drugs known to prolong the QT interval (e.g. Class IA and III anti-arrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see 'Special warnings and precautions for use').

Chelation complex formation

The simultaneous administration of Ciprobay and multivalent cation-containing medicinal products and mineral supplements (e.g. calcium, magnesium, aluminum, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids, and highly buffered drugs (e.g. didanosine tablets) containing magnesium, aluminum, or calcium reduce the absorption of ciprofloxacin. Consequently, 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.

Probenecid

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

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin resulting in a shorter time to reach maximum plasma concentrations. No effect was seen on the bioavailability of ciprofloxacin.

Omeprazole

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

Tizanidine

In a clinical study in healthy subjects, there was an increase in tizanidine serum concentrations (C_{max} increase: 7-fold, range: 4 to 21-fold; AUC increase: 10-fold, range: 6 to 24-fold) when given concomitantly with ciprofloxacin. Associated with the increased serum concentrations was a potentiated hypotensive and sedative effect (see 'Cytochrome

P450' in section 'Special warnings and precautions for use'). Tizanidine containing medicinal products must not be administered together with Ciprobay (see "'Contraindications'").

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.

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 measurents, is recommended during and shortly after co-administration of Ciprobay with phenytoin.

Methotrexate
Renal tubular transport of methotrexate may be inhibited by concomitant administration of Ciprobay, potentially leading to increased plasma levels of methotrexate and increased risk of methotrexate-associated toxic reactions. The concomitant use is not recommended.

NSAID
Animal studies have shown that the combination of very high doses of quinolones (gyrase inhibitors) and certain non-steroidal anti-inflammatory agents (but not acetylsalicylic acid) can provoke convulsions.

Cyclosporin
A transient rise in the concentration of serum creatinine was observed when ciprofloxacin and cyclosporin containing medicinal products were administered simultaneously. Therefore, it is frequently (twice a week) necessary to control the serum creatinine concentrations in these patients.

Vitamin K antagonists
Simultaneous administration of 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).

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

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 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.

4.6 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 animal studies, it cannot be excluded that the drug could cause damage to articular cartilage in the immature fetal 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 during breast-feeding (see 'Preclinical safety data').

4.7 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 'Undesirable effects'). 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 = 51621).

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

The ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under “not known”.
Not known: frequency cannot be estimated from the available data.

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 (lifethreatening)	
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Anaphylactic shock (lifethreatening) Serum sicknesslike 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 selfinjurious behavior, such as suicidal ideations / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behavior, such as suicidal ideations/thoughs and attempted or completed suicide)	
Nervous System Disorders#		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysesthesia Hypoesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperesthesia Intracranial hypertension (pseudotumor cerebri)	Peripheral neuropathy and polyneuropathy
Eye Disorders#			Visual disturbances	Visual color distortions	
Ear and Labyrinth Disorders#			Tinnitus Hearing loss	Hearing impaired	
Cardiac Disorders			Tachycardia		QT prolongation, ventricular arrhythmia, torsades de pointes * Kounis syndrome #
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 Erythema nodosum StevensJohnson syndrome (potentially lifethreatening) Toxic epidermal necrolysis (potentially lifethreatening)	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	Injection site reaction	Unspecific pain Feeling unwell Fever	Eedema Sweating (hyperhidrosis)	Gait disturbance	
Site Conditions#					
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level Increased amylase		International normalized ratio (INR) increased (in patients treated with Vitamin K antagonists)

* These events were reported during the postmarketing period and were observed predominantly among patients with further risk factors for QT prolongation (see 'Special warnings and precautions for use').
# Acute myocardial ischemia with or without myocardial infarction as part of a hypersensitivity reaction (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 disturbances of sense.
The following undesirable effects have a higher frequency category in the subgroups of patients receiving intravenous or sequential (intravenous to oral) treatment:

Common	Vomiting, Transient increase in transaminases, Rash
Uncommon	Thrombocytopenia, Thrombocytaemia, Confusion and disorientation, Hallucinations, Par- and dysaesthesia, Seizures, Vertigo, Visual disturbances, Hearing loss, Tachycardia, Vasodilatation, Hypotension, Transient hepatic impairment, Jaundice, Renal failure, Eedema
Rare	Pancytopenia, Bone marrow depression, Anaphylactic shock, Psychotic reactions, Migraine, Smell disorders, Hearing impaired, Vasculitis, Pancreatitis, Liver necrosis, Petechiae, Tendon rupture

<The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 14.0
(except for 'Mycotic superinfections' and 'Unspecific pain')>

Paediatric patients
The incidence of arthropathy, (arthralgia, arthritis) mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see 'Special warnings and precautions for use').

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 crytalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses.

Only a small quantity of ciprofloxacin (< 10 %) is eliminated by hemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones, ATC code: J01MA02

Mechanism of action:
As a fluoroquinolone antibacterial agent, the bactericidal action of ciprofloxacin results from the inhibition of both type II topoisomerase (DNA-gyrase) and topoisomerase IV, required for bacterial DNA replication, transcription, repair and recombination.

PK/PD relationship:
Efficacy mainly depends on the relation between the maximum concentration in serum (C_{max}) and the minimum inhibitory concentration (MIC) of ciprofloxacin for a bacterial pathogen and the relation between the area under the curve (AUC) and the MIC.

Mechanism of resistance:
In-vitro resistance to ciprofloxacin can be acquired through a stepwise process by target site mutations in both DNA gyrase and topoisomerase IV. The degree of cross-resistance between ciprofloxacin and other fluoroquinolones that results is variable. Single mutations may not result in clinical resistance, but multiple mutations generally result in clinical resistance to many or all active substances within the class.

Impermeability and/or active substance efflux pump mechanisms of resistance may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. All in-vitro mechanisms of resistance are commonly observed in clinical isolates. Resistance mechanisms that inactivate other antibiotics such as permeation barriers (common in Pseudomonas aeruginosa) and efflux mechanisms may affect susceptibility to ciprofloxacin. Plasmidmediated resistance encoded by qnr-genes has been reported.

Spectrum of antibacterial activity:
Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

In vitro susceptibility to ciprofloxacinThe prevalence of acquired resistance may vary geographically and with time for selected species and local information of resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Groupings of relevant species according to ciprofloxacin susceptibility (for Streptococcus species see section 4.4)

COMMONLY SUSCEPTIBLE SPECIES
Aerobic Gram-positive micro-organisms Bacillus anthracis (1)
Aerobic Gram-negative micro-organisms Aeromonas spp. Brucella spp. Citrobacter koseri Francisella tularensis Haemophilus ducreyi Haemophilus influenzae* Legionella spp. Moraxella catarrhalis* Neisseria meningitidis Pasteurella spp. Salmonella spp.* Shigella spp. * Vibrio spp. Yersinia pestis
Anaerobic micro-organisms Mobiluncus
Other micro-organisms Chlamydia trachomatis ($) Chlamydia pneumoniae ($) Mycoplasma hominis ($) Mycoplasma pneumoniae ($)
SPECIES FOR WHICH ACQUIRED RESISTANCE MAY BE A PROBLEM
Aerobic Gram-positive micro-organisms Enterococcus faecalis ($) Staphylococcus spp. *(2)

Aerobic Gram-negative micro-organisms Acinetobacter baumannii[+] Burkholderia cepacia [+]* Campylobacter spp.[+]* Citrobacter freundii* Enterobacter aerogenes Enterobacter cloacae * Escherichia coli* Klebsiella oxytoca Klebsiella pneumoniae* Morganella morganii*
Neisseria gonorrhoeae* Proteus mirabilis* Proteus vulgaris* Providencia spp. Pseudomonas aeruginosa* Pseudomonas fluorescens Serratia marcescens*
Anaerobic micro-organisms Peptostreptococcus spp. Propionibacterium acnes
INHERENTLY RESISTANT ORGANISMS
Aerobic Gram-positive micro-organisms Actinomyces Enteroccus faecium Listeria monocytogenes
Aerobic Gram-negative micro-organisms Stenotrophomonas maltophilia
Anaerobic micro-organisms Excepted as listed above
Other micro-organisms Mycoplasma genitalium Ureaplasma urealitycum

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

[+] Resistance rate ≥ 50% in one or more EU countries

($): Natural intermediate susceptibility in the absence of acquired mechanism of resistance

(1): Studies have been conducted in experimental animal infections due to inhalations of Bacillus anthracis spores; these studies reveal that antibiotics starting early after exposition avoid the occurrence of the disease if the treatment is made up to the decrease of the number

of spores in the organism under the infective dose. The recommended use in human subjects is based primarily on in-vitro susceptibility and on animal experimental data together with limited human data. Two-month treatment duration in adults with oral ciprofloxacin given at the following dose, 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

Film-coated tablets

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

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.

Comparison of the pharmacokinetic parameters for a twice a day and three times a day intravenous dose regimen indicated no evidence of drug accumulation for ciprofloxacin and its metabolites.

A 60-minute intravenous infusion of 200 mg ciprofloxacin or the oral administration of 250 mg ciprofloxacin, both given every 12 hours, produced an equivalent area under the serum concentration time curve (AUC).

A 60-minute intravenous infusion of 400 mg ciprofloxacin every 12 hours was bioequivalent to a 500 mg oral dose every 12 hours with regard to AUC.

The 400 mg intravenous dose administered over 60 minutes every 12 hours resulted in a C_{max} similar to that observed with a 750 mg oral dose.

A 60-minute infusion of 400 mg ciprofloxacin every 8 hours is equivalent with respect to AUC to 750 mg oral regimen given every 12 hours.

Distribution

Protein binding of ciprofloxacin is low (20-30%). Ciprofloxacin is present in plasma largely in a non-ionised form and has a large steady state distribution volume of 2-3 L/kg body weight. Ciprofloxacin reaches high concentrations in a variety of tissues such as lung (epithelial fluid, alveolar macrophages, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid), and the urogenital tract (urine, prostate, endometrium) where total concentrations exceeding those of plasma concentrations are reached.

Metabolism

Low concentrations of four metabolites have been reported, which were identified as: desethyleneciprofloxacin (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.

Film-coated tablets

The serum elimination half-life in subjects with normal renal function is approximately 47 hours.

Exc	etion of ciprofloxacin (% of dose)	
	Oral Administration	
	Urine	Faeces
Ciprofloxacin	44.7	25.0
Metabolites (M_1-M_4)	11.3	7.5

Solution for Infusion

Excretion of ciprofloxacin (% of dose)		
	Intravenous Administration	
	Urine	Faeces

Ciprofloxacin	61.5	15.2
Metabolites (M_1-M_4)	9.5	2.6

Renal clearance is between 180-300 mL/kg/h and the total body clearance is between 480600 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 weightbearing 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 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 (with 0.9% NaCl)
Lactic acid,
Sodium chloride,
Hydrochloric acid concentrated, Water for injections.

Incompatibilities

Ciprobay solution for infusion (0.9% NaCl)

Ciprobay solution for infusion (0.9% NaCl)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 Ciprobay solutions for infusion (0.9% NaCl) are mixed with compatible solutions for infusion, 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 solution for infusion must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding, and discoloration.

Incompatibility appears with all solutions for infusion/medicinal products that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially on combination with solutions adjusted to an alkaline pH (pH of the Ciprobay solutions for infusion (0.9% NaCl): 3.9 – 4.5).

Shelf life

Please refer to label.

Special precautions for storage
Ciprobay film-coated tablets
Do not store above 30°C

Ciprobay solution for infusion
Not to be stored above 30 °C = 86 °F

Protect from light. Do not refrigerate or freeze.

As the infusion solution is sensitive to light, only remove the bottles from the folding box for use. In daylight the full efficacy of the solution is guaranteed over a period of 3 days.

<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.>

Glass Bottles (solution for infusion, 0.9% NaCl)
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.

Nature and contents of container
Ciprobay film-coated tablets
Blister packs containing 10 film-coated tablets per blister.

Ciprobay solution for infusion (with 0.9% NaCl)
Ciprobay 100: 1 glass vial of 50ml infusion solution containing 100mg ciprofloxacin
Ciprobay 200: 1 glass vial of 100ml infusion solution containing 200mg ciprofloxacin
Ciprobay 400: 1 glass vial of 200ml infusion solution containing 400mg ciprofloxacin

Not all pack sizes and presentations are available in all markets.

Manufactured by
Ciprobay film-coated tablets
Bayer HealthCare Manufacturing S.r.l.
Via delle Groane 126
20024 Garbagnate Milanese
Italy

Ciprobay solution for infusion (with 0.9% NaCl)
Bayer AG
D-51368 Leverkusen,
Germany

Date of Revision
Feb 2026

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.