Prescribing Information

Bactiflox 250/500/750, Lactab

Composition

Active substance

Ciprofloxacin as C. hydrochloride.

Excipients

Microcrystalline cellulose, maize starch, crospovidone, colloidal anhydrous silica, magnesium stearate, hypromellose (E464), macrogol 6000, colouring agent titanium dioxide (E171), talc.

Pharmaceutical form and amount of active substance per unit

Bactiflox 250 Lactab: 1 film-coated tablet contains 250 mg ciprofloxacin as ciprofloxacin HCl H_2O.

Bactiflox 500 Lactab: 1 film-coated tablet contains 500 mg ciprofloxacin as ciprofloxacin HCl H_2O.

Bactiflox 750 Lactab: 1 film-coated tablet contains 750 mg ciprofloxacin as ciprofloxacin HCl H_2O.

Indications/Possibilities for use

Bactiflox Lactab is indicated for the treatment of the following infections. Special attention should be paid to the available information on resistance before commencing therapy.

Adults

- lower respiratory tract infections caused by Gram-negative bacteria
- exacerbations of chronic obstructive pulmonary disease (COPD)
- bronchopulmonary infections in cystic fibrosis or in bronchiectasis
- pneumonia
- chronic suppurative otitis media
- acute exacerbation of chronic sinusitis, especially when caused by Gram-negative bacteria
- urinary tract infections
- infections of the genital tract (cf. “Warnings and precautions”)
- gonococcal urethritis and gonococcal cervicitis caused by susceptible *Neisseria gonorrhoeae*
- epididymo-orchitis including cases caused by susceptible *Neisseria gonorrhoeae*
- pelvic inflammatory disease (PID), including cases caused by *Neisseria gonorrhoeae*
- infections of the gastrointestinal tract (e.g. travellers’ diarrhoea)
- intraabdominal infections

- infections of the skin and soft tissue caused by Gram-negative bacteria
- malignant external otitis
- infections of the bones and joints
- prophylaxis of invasive infections caused by *Neisseria meningitidis*
- inhalation of anthrax pathogens (post-exposure prophylaxis and curative treatment)

Bactiflox Lactab can be used for the treatment of neutropenic patients with fever, if there is a suspicion that the fever is caused by a bacterial infection.

Paediatric population

- Bronchopulmonary infections in cystic fibrosis caused by *Pseudomonas aeruginosa*
- In children aged 1 year and older, as a third-choice agent for the treatment of complicated urinary tract infections, as well as for pyelonephritis caused by *E. coli*. The indication for treatment should be established only after consultation with a specialist, i.e. an infectiologist or paediatrician specialised in infectiology.

Bactiflox Lactab can also be used to treat severe infections in children and adolescents, when deemed necessary.

Treatment should be initiated only by physicians who are experienced in the treatment of cystic fibrosis and/or severe infections in children and adolescents (cf. “Warnings and precautions” and “Properties/Effects, Pharmacodynamics”). Clinical studies have been performed in the above-mentioned indications. For other indications, clinical experience is limited.

Children under 6 years of age should be treated with a suitable dosage form.

Anthrax (adults and children)

For post-exposure prophylaxis and treatment of anthrax after inhalation of the pathogen *Bacillus anthracis*. The efficacy of ciprofloxacin in anthrax has been demonstrated in animal experiments (see section "Properties/Effects"). In children, adolescents and pregnant women, after determining the resistance pattern of the *Bacillus anthracis* strain involved, the possibility of switching therapy to (amino) penicillins should be reviewed.

Official recommendations on the appropriate use of antibiotics should be followed, especially recommendations on use to prevent the increase of antibiotic resistance.

Posology/Administration

Posology and duration of treatment in adults

The duration of treatment depends on the severity of the illness and on the clinical and bacteriological course.

As a general rule, treatment should be strictly continued for at least 3 days after defervescence or resolution of clinical symptoms.

The usual dosage for oral administration in single/daily doses

Indication	Lactabs	Total duration of treatment (potentially including initial parenteral treatment with ciprofloxacin)
Infections of the lower respiratory tract	2× 500 mg to 2× 750 mg	7 to 14 days
Infections of the upper respiratory tract		
Acute exacerbation of chronic sinusitis	2× 500 mg to 2× 750 mg	7 to 14 days
Chronic suppurative otitis media	2× 500 mg to 2× 750 mg	7 to 14 days
Malignant external otitis	2× 750 mg	28 days up to 3 months
Urinary tract infections		
Uncomplicated cystitis	2× 250 mg to 2× 500 mg In pre-menopausal women, 500 mg can be given as a single dose.	3 days
Complicated cystitis, uncomplicated pyelonephritis	2× 500 mg	7 days
Complicated pyelonephritis	2× 500 mg to 2× 750 mg	at least 10 days; a treatment period beyond 21 days is possible under certain circumstances (such as abscesses)
Prostatitis	2× 500 mg to 2× 750 mg	2 to 4 weeks (acute) to 4 to 6 weeks (chronic)
Infections of the genital tract		
Gonococcal urethritis and gonococcal cervicitis (cf. "Warnings and precautions")	500 mg as a single dose	1 day (single dose)
Epididymo-orchitis and pelvic inflammatory disease	2× 500 mg to 2× 750 mg	at least 14 days
Infections of the gastrointestinal tract and intraabdominal infections		
Diarrhoea caused by bacterial pathogens including *Shigella spp.* other than *Shigella dysenteriae* type 1 and empirical treatment of severe travellers' diarrhoea	2× 500 mg	1 day
Diarrhoea caused by *Shigella dysenteriae* type 1	2× 500 mg	5 days
Diarrhoea caused by *Vibrio cholerae*	2× 500 mg	3 days
Typhoid fever	2× 500 mg	7 days
Intraabdominal infections due to Gram-negative bacteria	2× 500 mg to 2× 750 mg	5 to 14 days

Infections of the skin and soft tissue	2× 500 mg to 2× 750 mg	7 to 14 days
Bone and joint infections	2× 500 mg to 2× 750 mg	3 months maximum
Neutropenic patients with fever, when there is a suspicion that the fever is caused by a bacterial infection. Ciprofloxacin should be combined with suitable antibacterial agents in accordance with official recommendations.	2× 500 mg to 2× 750 mg	Therapy should be continued over the entire period of neutropenia
Prophylaxis of invasive infections due to *Neisseria meningitidis*	500 mg as a single dose	1 day (single dose)

Although efficacy in clinical studies has been demonstrated, ciprofloxacin is not regarded as the first-choice agent for the treatment of suspected or diagnosed pneumonia caused by *Streptococcus pneumoniae*.

With regard to AUC, a 60-minute infusion with 400 mg ciprofloxacin, every 8 hours, is equivalent to an oral dose of 750 mg ciprofloxacin every 12 hours.

Posology and duration of treatment in children and adolescents

Indication	Daily dose in mg	Total duration of treatment (potentially including initial parenteral treatment with Bactiflox Lactab)
Cystic fibrosis in children and adolescents (5-17 years) with acute infectious episodes	2× 20 mg/kg body weight with a maximum single dose of 750 mg	10 to 14 days
Complicated urinary tract infections and pyelonephritis by *E. coli*	2× 10-20 mg/kg body weight with a maximum single dose of 750 mg	10 to 21 days
Other severe infections	2× 20 mg/kg body weight with a maximum single dose of 750 mg	Depending on the type of infections

No experience is available on dosage in children with impaired renal or hepatic function.

Posology in elderly patients

Elderly patients should receive the lowest possible dosage. In the event of impaired renal function, the dosage should be adjusted accordingly (cf. “Special dosage instructions” below).

Posology and duration of treatment in anthrax

Adults, adolescents and children:

Treatment should commence *immediately* after suspected or confirmed inhalation of anthrax pathogens and initially with intravenous ciprofloxacin. In children, adolescents and pregnant

women, after determining the resistance pattern of the *Bacillus anthracis* strain involved, the possibility of switching therapy to (amino) penicillins should be reviewed.
Therapeutic efficacy can be assumed after use of the following dosages based on pathogen susceptibility *in vitro* and anticipated plasma levels in each case (see also section "Properties/Effects").

Adults	500 mg twice daily.
Children/adolescents	10-15 mg/kg body weight twice daily. The maximum daily dose in children should not exceed 500 mg (maximum daily dose: 1,000 mg ciprofloxacin).

For post-exposure prophylaxis commenced intravenously or treatment after inhalation of anthrax pathogens, a switch can be made to continued oral treatment depending on the clinical picture. The total duration of treatment (intravenous and oral) is 60 days.

Special dosage instructions - adults

Dosage in impaired renal function

Degree of renal dysfunction		
Creatinine clearance	Serum creatinine value	Maximum daily dose
30-60 mL/min/1.73 m²	1.4-1.9 mg/100 mL (124-168 µmol/L)	1,000 mg
<30 mL/min/1.73 m²	>2.0 mg/100 mL (177 µmol/L)	500 mg

Dosage in impaired renal function and haemodialysis

Creatinine clearance 30-60 ml/min/1.73 m²

Dosage according to the above regimen.

Creatinine clearance <30 mL/min/1.73 m²

Bactiflox Lactab should be given on the dialysis days, after dialysis. In this scenario, the dosage should be as per the above table for creatinine clearance <30 mL/min/1.73 m².

Dosage in impaired renal function and continuous ambulatory peritoneal dialysis

1 x 500 mg Bactiflox Lactab or 2 x 250 mg Bactiflox Lactab.

Dosage in impaired hepatic function

In patients with impaired hepatic function, ciprofloxacin elimination is only slightly altered; no dose adjustment is required. If hepatic and renal functions are concomitantly impaired, the dosage should be adjusted to the degree of renal dysfunction.

Method of administration

Bactiflox Lactab are to be swallowed unchewed with some liquid and can be taken independently of meals. Ingestion on an empty stomach accelerates absorption. Bactiflox Lactab should not be taken with dairy products (e.g. milk or yoghurt) or mineral-enriched drinks (e.g. calcium-enriched orange juice) (see also section “Interactions”).

In severe cases or if the patient is unable to take tablets, it is recommended that therapy be commenced with intravenously administered ciprofloxacin, until the switch to oral administration is possible. Cf. section “Instructions for handling”.

Contraindications

Hypersensitivity to ciprofloxacin, any other active substance of the quinolone type or to any of the excipients in the composition.

Ciprofloxacin should not be used in pregnant or lactating women until further information becomes available. With regard to use in anthrax, see sections "Indications/Possibilities for use” and “Pregnancy/Lactation”.

Children and adolescents should not be treated with ciprofloxacin until completion of the growth phase, since, based on results from animal trials, articular cartilage damage cannot be excluded in the still immature organism. With regard to use in cystic fibrosis, anthrax, complicated urinary tract infections and *E. coli*-induced pyelonephritis, see section “Warnings and precautions”.

The combination of ciprofloxacin and tizanidine is contraindicated, as ciprofloxacin may increase the serum level of tizanidine to such an extent that clinically relevant adverse drug reactions to tizanidine (hypotension, somnolence, light-headedness, nausea, vomiting, hepatic dysfunction, miosis, respiratory depression, coma, restlessness) might occur.

Warnings and precautions

Cardiac disorders

In some patients, ciprofloxacin causes a prolongation of the QT interval in the ECG (see also section “Undesirable effects”). As women are more prone than men to a prolonged QTc baseline value, they may be more sensitive to QTC-prolonging co-medications. In addition, elderly patients may be more sensitive to drug-associated effects on the QT interval. In patients treated with medicinal products that can prolong the QT interval (e.g. Class IA or Class III antiarrhythmics, tricyclic antidepressants, macrolides or antipsychotics), concomitant use of ciprofloxacin should proceed with caution. Similarly, concomitant use of ciprofloxacin should proceed with caution in patients at risk of QT prolongation (e.g. in cases of congenital QT syndrome, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and in cases of heart failure, myocardial infarction or bradycardia).

Severe infections and mixed infections with Gram-positive and anaerobic pathogens

Ciprofloxacin monotherapy is not suitable for the treatment of severe infections and those infections which might be caused by Gram-positive or anaerobic pathogens. In such cases, ciprofloxacin must be combined with other appropriate antibacterial agents.

Streptococcal infections (including Streptococcus pneumoniae)

Ciprofloxacin is not recommended for the treatment of streptococcal infections due to its insufficient efficacy.

Genital tract infections

Genital tract infections may be caused by fluoroquinolone-resistant *Neisseria gonorrhoeae*. If such infections are caused, or suspected of being caused, by *Neisseria gonorrhoeae,* it is particularly important to obtain information on the local prevalence of resistance to ciprofloxacin and confirm it by microbiological resistance testing.

Paediatric population

Treatment of children and adolescents should be initiated only after a careful benefit/risk assessment. In particular, possible undesirable effects on joints and/or the surrounding tissue must be considered. As is known from other gyrase inhibitors, ciprofloxacin causes damage to the weight-bearing joints of juvenile animals. The evaluation of safety data from adolescent patients with cystic fibrosis or complicated urinary tract infections showed no indications of permanent articular/cartilage damage.

The current data in children and adolescents support the use of ciprofloxacin in acute infectious episodes of cystic fibrosis caused by *P. aeruginosa*, in anthrax, complicated infections of the urinary tract, as well as *E. coli*-induced pyelonephritis (see sections “Indications/Possibilities for use” and “Posology/Administration”). Ciprofloxacin is not recommended for other indications.

Gastrointestinal tract

Severe and persistent diarrhoea during or after treatment can conceal a pseudomembranous colitis which requires immediate treatment. In such cases ciprofloxacin must be discontinued and appropriate diagnostic and therapeutic procedures initiated (e.g. oral vancomycin 4× 250 mg daily). Antiperistaltic agents are contraindicated.

Hepatobiliary system

Cases of hepatocellular necrosis and life-threatening hepatic failure have been reported in association with ciprofloxacin (see section “Undesirable effects”). Treatment with ciprofloxacin should be discontinued if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus or tender abdomen. Hepatic function should be checked at signs of dysfunction. Transiently elevated transaminase levels, elevated concentrations of alkaline phosphatase and cholestatic jaundice may occur, especially in patients with a history of hepatic dysfunction.

Hypersensitivity

In very rare cases, anaphylactic/anaphylactoid reactions (e.g. facial, vascular and laryngeal oedema; dyspnoea and even life-threatening shock) have been reported, sometimes even after ingestion of the initial dose. In such cases, ciprofloxacin must be discontinued immediately; medical treatment (e.g. shock therapy) is required.

Photosensitisation

In rare cases, ciprofloxacin can cause photosensitivity reactions or phototoxic reactions. Patients should avoid exposing themselves to sunlight for prolonged periods during therapy with ciprofloxacin. If this is not possible, a sun protection cream with a sufficiently high sun protection factor should be used and clothing to cover the skin should be worn.

Central nervous system

Fluoroquinolones such as ciprofloxacin may trigger seizures or lower the seizure threshold. If seizures occur, treatment with ciprofloxacin should be discontinued. In patients with epilepsy and patients with other pre-existing damage to the central nervous system (e.g. reduced seizure threshold, history of seizures, reduced cerebral perfusion, changes in brain structure or stroke), ciprofloxacin should be used only after careful benefit-risk assessment, as these patients are at risk of possible adverse central nervous reactions. Cases of status epilepticus have been reported. Psychiatric reactions may occur even after first administration of ciprofloxacin. In rare cases, depression or psychosis can progress to self-harming behaviour such as suicide or attempted suicide. In such cases, ciprofloxacin must be discontinued immediately, a doctor consulted and appropriate measures instituted.

Peripheral neuropathy

Cases of sensory or motor-sensory polyneuropathy, which have led to paraesthesia, hypoaesthesia or dysaesthesia, have been reported in patients treated with fluoroquinolones, including ciprofloxacin. Such neuropathies can manifest rapidly. Patients on treatment with ciprofloxacin should be instructed to discontinue treatment and to contact their physician if symptoms of neuropathy (pain, burning, tingling, numbness or weakness) occur. These measures reduce the possible risk of developing irreversible nerve damage.

Musculoskeletal system

Ciprofloxacin should be used with caution in patients with myasthenia gravis, as symptoms may deteriorate (see section “Undesirable effects”).

Ciprofloxacin should generally not be used in patients with a positive history of tendon disease/complaints associated with quinolone treatment. Nevertheless, in very rare cases after microbiological confirmation of the pathogen and careful benefit-risk assessment, ciprofloxacin can be prescribed to these patients for the treatment of certain severe infections, particularly after standard therapy has failed or when bacterial resistance is present, where the microbiological data

justify the use of ciprofloxacin. Tendinitis and tendon rupture (especially the Achilles tendon), sometimes bilateral, may occur during treatment with ciprofloxacin, even within the first 48 hours after the start of treatment. Tendinitis and tendon rupture may even occur only after several months upon completion of ciprofloxacin therapy. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids. At any sign of tendinitis (e.g. painful swelling, inflammation), treatment with ciprofloxacin should be discontinued immediately. Care should be taken to keep the affected limb immobilised.

Cytochrome P450

Ciprofloxacin is a moderately potent inhibitor of cytochrome P450 1A2 enzymes. Caution should be exercised when co-administering medicinal products that are metabolised by these same enzymes (e.g. theophylline, methylxanthine, caffeine, tizanidine, duloxetine, clozapine, ropinirole or olanzapine). Elevated plasma levels and drug-specific adverse reactions may occur due to inhibited clearance of these medicinal products (see sections “Contraindications” and “Interactions”).

Other warnings and precautions

Long-term and repeated use can lead to superinfections with resistant bacteria or yeast-like fungi. Vigilance is required for the possibility of cross-resistance between ciprofloxacin and other fluoroquinolones.

As ciprofloxacin is excreted primarily via the urine and, to a lesser extent, via the hepatobiliary system, caution should be exercised in patients with impaired renal function. Crystalluria has been reported in rare cases, which is why patients should be instructed to drink sufficient amounts.

Patients with existing glucose-6-phosphate dehydrogenase deficiency, or a past family history thereof, are prone to haemolytic reactions to quinolones. Therefore, ciprofloxacin should only be used with caution in these patients.

Interactions

Medicinal products that can prolong the QT interval

Caution should be exercised when co-administering ciprofloxacin with medicinal products that can prolong the QT interval (Class IA or Class III antiarrhythmics, tricyclic antidepressants, macrolides, psychotropic agents), as ciprofloxacin can have an additive effect on QT prolongation.

Interactions with active substances metabolised via cytochrome P450 1A2 isoenzymes

Ciprofloxacin is a moderately potent inhibitor of cytochrome P450 1A2 enzymes. Caution should be exercised when co-administering medicinal products that are metabolised by these same enzymes, e.g. theophylline, methylxanthine, caffeine, tizanidine, duloxetine, clozapine, ropinirole or olanzapine (see section “Warnings and precautions”).

Tizanidine

Tizanidine must not be administered together with ciprofloxacin. In healthy subjects, co-administration of ciprofloxacin and tizanidine led to an increase in tizanidine serum levels. The C_{max} value increased 7-fold (individual values ranging from 4- to 21-fold); that of AUC by 10-fold (individual values ranging from 6- to 24-fold). The increase in tizanidine levels was associated with potentiation of the hypotensive and sedative effects, such as nausea, vomiting, hepatic dysfunction, miosis, respiratory depression, coma or restlessness (see “Contraindications” and “Warnings and precautions”).

Duloxetine

Concomitant ingestion of duloxetine with potent inhibitors of the CYP450 1A2 isozyme, such as fluvoxamine, led to an increase in the C_{max} and AUC values for duloxetine. Although there are still no reports available on any such interaction between ciprofloxacin and duloxetine, such a one might occur upon concomitant administration of ciprofloxacin and duloxetine.

Clozapine

Concomitant administration of 250 mg ciprofloxacin and clozapine for 7 days led to an increase in serum values for clozapine and its metabolite N-desmethylclozapine by 29% and 31%, respectively. Clinical surveillance and appropriate adjustment of the clozapine dosage during and shortly after treatment with ciprofloxacin is advised.

Ropinirole

Within the framework of a clinical study, concomitant ingestion of ciprofloxacin with ropinirole (a moderate inhibitor of CYP450 1A2) led to an increase in C_{max} and AUC for ropinirole by 60% and 84%, respectively. Although treatment with ropinirole was generally well tolerated, individual case reports of adverse drug reactions give rise to the suspicion that concomitant ingestion of ciprofloxacin and ropinirole may lead to an interaction between these two agents. Surveillance and appropriate adjustment of the ropinirole dosage during and shortly after treatment with ciprofloxacin are advised.

Lidocaine

In healthy subjects, ciprofloxacin reduces the elimination of intravenously administered lidocaine (another moderate inhibitor of CYP450 1A2) by 22%. Although administration of intravenous lidocaine was well tolerated, an interaction with ciprofloxacin – together with associated adverse drug reactions – cannot be excluded.

Sildenafil

Upon concomitant administration of 500 mg ciprofloxacin and 50 mg sildenafil in healthy subjects, the C_{max} and AUC of sildenafil were increased approximately twofold. Therefore, caution should be exercised when co-prescribing sildenafil and ciprofloxacin.

Chelation complex formation

Concomitant use of ciprofloxacin (oral) with iron, sucralfate, antacids, highly buffered preparations (e.g. antiretroviral agents) containing magnesium, aluminium or calcium, or phosphate-binding polymers (e.g. sevelamer or lanthanum carbonate) reduces the absorption of ciprofloxacin. Consequently, ciprofloxacin should be administered either 1-2 hours before or 4 hours after these preparations. This restriction does not apply to antacids of the H_2-receptor blocker type.

Theophylline

Concurrent administration of ciprofloxacin and theophylline can lead to an undesirable rise in serum theophylline concentrations to within toxic ranges. This can lead to theophylline-induced adverse reactions that may rarely be life-threatening or fatal. If concomitant use of both preparations cannot be avoided, the serum concentration of theophylline should be checked and its dosage reduced accordingly.

Other xanthine derivatives

Upon co-administration of ciprofloxacin and caffeine or pentoxifylline (oxpentifylline), raised serum concentrations of these derivatives have been described.

Phenytoin

Concomitant administration of ciprofloxacin and phenytoin may lead to increased or reduced phenytoin serum concentrations, which is why monitoring of drug levels is recommended.

NSAIDs

From animal studies, it is known that the combination of very high doses of quinolones (gyrase inhibitors) and some non-steroidal anti-inflammatory drugs (e.g. fenbufen, but not acetylsalicylic acid) may cause seizures.

Ciclosporin

Upon co-administration of ciprofloxacin and ciclosporin, a transient rise in the serum creatinine concentration has been observed in individual cases. For this reason, close monitoring (twice weekly) of the serum creatinine level is required in these patients.

Vitamin K antagonists

Simultaneous administration of ciprofloxacin and a vitamin K antagonist (e.g. warfarin, acenocoumarol, phenprocoumon or fluindione) may potentiate the anticoagulant effect. The risk may vary depending on the underlying infection, age and general status of the patient, so that it may be difficult to assess the effect of ciprofloxacin on the increased INR (International Normalised Ratio). The INR should be monitored frequently during and immediately after co-administration of ciprofloxacin and a vitamin K antagonist.

Oral antidiabetics

Individual cases of hypoglycaemia have been observed upon concomitant administration of ciprofloxacin and oral antidiabetics (mainly sulphonylureas, e.g. glibenclamide and glimepiride), probably caused by enhanced efficacy of the antidiabetic agents.

Probenecid

Probenecid affects the renal secretion of ciprofloxacin. Co-administration of probenecid (1,000 mg) and ciprofloxacin (500 mg) increased the serum concentration of ciprofloxacin by approximately 50% whilst the elimination half-life remained unchanged, which should be taken into account in patients concomitantly receiving these two medicinal products.

Metoclopramide

Metoclopramide accelerates the absorption of ciprofloxacin, whereby peak plasma concentrations are reached more rapidly. The bioavailability of ciprofloxacin is not affected.

Omeprazole

Concomitant administration of ciprofloxacin and omeprazole causes a slight reduction in the C_{max} and AUC of ciprofloxacin.

Methotrexate

Upon concomitant administration of ciprofloxacin and methotrexate, the plasma levels of methotrexate may be increased due to competitive inhibition of its tubular secretion. As this may lead to an increased risk of methotrexate-related toxic reactions, patients should be carefully monitored.

Tacrolimus

Particular caution should be exercised in patients concomitantly treated with tacrolimus and ciprofloxacin, as the known nephrotoxicity or neurotoxicity of both substances might be aggravated as a result of co-administration.

Dairy products and calcium-rich food

Ciprofloxacin should not be taken together with dairy products or calcium-rich foods (e.g. milk, yoghurt, calcium-enriched fruit juice), as this might reduce the absorption of ciprofloxacin. On the other hand, the absorption of ciprofloxacin is not impaired by the calcium content of a normal meal.

Pregnancy/Lactation

Pregnancy

Animal trials have revealed no indications of teratogenic effects, but there is a possibility of damage to growing cartilage. Ciprofloxacin passes into umbilical cord blood and amniotic fluid. Ciprofloxacin should not be used during pregnancy unless clearly indicated. For preventive use after exposure to anthrax pathogens, see “Indications/Possibilities for use”.

Breast-feeding

Ciprofloxacin was detectable in human milk at similar concentrations as in maternal serum. Due to the possibility of damage to the growing cartilage, ciprofloxacin should not be used during breast-feeding.

Effects on ability to drive and use machines

Due to the various reactions that occur in some individuals, the ability to drive or use machines may be impaired. This particularly applies in interaction with alcohol.

Undesirable effects

The following adverse drug reactions have been observed with ciprofloxacin in clinical studies (n = 51,621) as well as in post-marketing surveillance:

Infections

Uncommon (0.1-1%): mycotic superinfections.

Rare (0.01-0.1%): antibiotic-associated colitis (in very rare cases, a fatal outcome is possible).

Blood and lymphatic system disorders

Uncommon (0.1-1%): eosinophilia.

Rare (0.01-0.1%): leukopenia, anaemia, neutropenia, leukocytosis, thrombocytopenia, thrombocythaemia.

Very rare (<0.01%): haemolytic anaemia, agranulocytosis, pancytopenia (life-threatening), bone marrow depression (life-threatening).

Immune system disorders

Uncommon (0.1-1%): skin reactions (see “Skin and subcutaneous tissue disorders”).

Rare (0.01-0.1%): allergic reactions, allergic oedema/angioedema.

Very rare (<0.01%): anaphylactic reactions, drug fever, anaphylactic shock (life-threatening, sometimes even after the first dose), serum sickness-type hypersensitivity reactions.

Metabolism and nutrition disorders

Rare (0.01-0.1%): hyperglycaemia, hypoglycaemia

Psychiatric disorders

Uncommon (0.1-1%): psychomotor hyperactivity/agitation.

Rare (0.01-0.1%): confusion and disorientation, states of anxiety, nightmares, depression (and even self-harming behaviour such as suicidal thoughts and suicide or suicidal attempt), hallucinations.

Very rare (<0.01%): psychotic reactions (and even self-harming behaviour such as suicidal thoughts and suicide or suicidal attempt).

Nervous system disorders

Uncommon (0.1-1%): headache, light-headedness, sleep disorders, taste disorders, fatigue, insomnia.

Rare (0.01-0.1%): paraesthesia, dysaesthesia, hypoaesthesia, tremor, seizures (incl. status epilepticus), vertigo.

Very rare (<0.01%): migraine, impaired coordination, parosmia, hyperaesthesia, intracranial hypertension (pseudotumor cerebri).

Post-marketing reports: peripheral neuropathy, polyneuropathy, anosmia (generally reversible upon discontinuation of the medication), stabbing pain.

Eye disorders

Rare (0.01-0.1%): visual disturbances.

Very rare (<0.01%): visual colour distortions, diplopia.

Ear and labyrinth disorders

Rare (0.01-0.1%): tinnitus, hearing loss.

Very rare (<0.01%): hearing impaired.

Cardiac disorders

Rare (0.01-0.1%): tachycardia, syncope.

Post-marketing reports: QT interval prolongation, ventricular arrhythmia, torsade de pointes. These undesirable effects have been mainly observed in patients with other risk factors for QT interval prolongation.

Vascular disorders

Rare (0.01-0.1%): vasodilation, hypotension.

Very rare (<0.01%): vasculitis, hot flushes.

Post-marketing reports: hypertension.

Respiratory, thoracic and mediastinal disorders

Rare (0.01-0.1%): dyspnoea (including asthma attacks).

Very rare (<0.01%): chest pain.

Gastrointestinal disorders

Common (1-10%): nausea, diarrhoea, indigestion, loss of appetite.

Uncommon (0.1-1%): vomiting, pain in the gastrointestinal region/abdomen, dyspepsia, flatulence.

Very rare (<0.01%): pancreatitis, pseudomembranous colitis.

Hepatobiliary disorders

Uncommon (0.1-1%): transaminases increased, bilirubinaemia.

Rare (0.01-0.1%): hepatic dysfunction, jaundice, (non-infectious) hepatitis.

Very rare (<0.01%): hepatocellular necrosis (in very rare cases, progressing to life-threatening hepatic failure).

Skin and subcutaneous tissue disorders

Uncommon (0.1-1%): rash, pruritus, macropapular rash, urticaria.

Rare (0.01-0.1%): photosensitivity reactions, blistering, hyperpigmentation.

Very rare (<0.01%): petechiae, erythema multiforme minor, haemorrhagic bullae, erythema nodosum, Stevens-Johnson syndrome (potentially life-threatening), toxic epidermal necrolysis (potentially life-threatening).
Post-marketing reports: Lyell's syndrome, acute generalised exanthematous pustulosis (AGEP).
Musculoskeletal and connective tissue disorders
Uncommon (0.1-1%): arthralgia.
Rare (0.01-0.1%): myalgia, arthritis*, increased muscle tone, cramps.
Very rare (<0.01%): muscular weakness, exacerbation of symptoms in patients with myasthenia gravis, tendinitis, partial or complete tendon rupture (predominantly the Achilles tendon; see "Warnings and precautions"), leg and back pain, tendovaginitis.
* These frequency data are based on study data in adults. Occurrence of arthropathy is common in children (cf. "Warnings and precautions").
Renal and urinary disorders
Uncommon (0.1-1%): renal dysfunction.
Rare (0.01-0.1%): renal failure, haematuria, crystalluria, interstitial nephritis.
General disorders and administration site conditions
Uncommon (0.1-1%): nonspecific pain, malaise, fever.
Rare (0.01-0.1%): oedema, sweating.
Very rare (<0.01%): gait disturbances, phlebitis, general asthenia
Investigations
Uncommon (0.1-1%): alkaline phosphatase increased.
Rare (0.01-0.1%): prothrombin levels abnormal, lipase and amylase levels increased.
Post-marketing reports: increased INR (International Normalised Ratio) in patients on treatment with vitamin K antagonists.
The following undesirable effects have occurred with greater frequency in the subgroup of patients receiving parenteral or sequential treatment:
Common: vomiting, transaminase levels transiently increased, rash.
Uncommon: thrombocytopenia, thrombocythaemia, confusion and disorientation, hallucinations, paraesthesia, dysaesthesia, seizures, vertigo, visual disturbances, numbness, tachycardia, vasodilation, hypotension, transient hepatic dysfunction, jaundice, renal dysfunction, oedema.
Rare: pancytopenia, myelosuppression, anaphylactic shock, psychotic reactions, migraine, parosmia, hearing impaired, vasculitis, pancreatitis, hepatocellular necrosis, petechiae, tendon rupture.

Overdose
Symptoms

In the event of an acute, excessive overdose, reversible renal toxicity has been observed in some cases.

Measures

Apart from the routine emergency measures, monitoring of renal function and the urinary pH value is recommended, together with acidification, if required, to prevent crystalluria, as well as giving antacids containing calcium or magnesium, which reduce the absorption of ciprofloxacin. Only a small percentage of ciprofloxacin (<10%) is removed from the body by haemodialysis or peritoneal dialysis. Adequate hydration must be ensured to avoid crystalluria.

Properties/Effects

ATC code: J01MA02

Bactiflox Lactab (Ciprofloxacin) is a synthetic antibiotic from the quinolone group.

Mechanism of action

As a fluoroquinolone antibacterial agent, ciprofloxacin has a bactericidal action resulting from the inhibition of topoisomerase II (DNA gyrase) and topoisomerase IV. Both enzymes are required for bacterial DNA replication, transcription, recombination and repair.

Ciprofloxacin prevents the transcription of information from the chromosome necessary for normal bacterial metabolism. This leads to a rapid decrease in bacterial proliferation capacity.

Furthermore, ciprofloxacin is characterised by the fact that, due to its particular mode of action, there is no general parallel resistance to any other antibiotic apart from the quinolone group. Thus, ciprofloxacin is in part also effective against bacteria that are resistant, for example, to aminoglycosides, penicillins, cephalosporins, tetracyclines and other antibiotics.

Resistance

The development of resistance against ciprofloxacin - as against other quinolones - has been observed in *Staphylococcus* spp. This particularly applies to methicillin-resistant strains of *S. aureus*. Increased resistance has also been described for *Pseudomonas aeruginosa*. A careful analysis of the literature shows that patients at particular risk are those requiring long-term antibiotic therapy, such as in cases of cystic fibrosis or osteomyelitis.

The situation should be regarded as similar for patients at particular risk of infection who require intensive antibiotic therapy for prophylactic or therapeutic reasons (e.g. leukaemia patients undergoing selective suppression of the intestinal flora; polytraumatised or surgical patients requiring longer-term intensive medical measures).

Resistance mechanism

In vitro resistance to ciprofloxacin can develop through a stepwise mutation process of DNA gyrase and topoisomerase IV. The degree of resultant cross-resistance between ciprofloxacin and other fluoroquinolones is variable. Single mutations do not usually result in clinical resistance, whereas

multiple mutations generally lead to clinical resistance to many or all active substances within the substance 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 qnr-genes has been reported.

Resistance mechanisms that inactivate penicillins, cephalosporins, aminoglycosides, macrolides and tetracyclines do not necessarily reduce the antibacterial efficacy of ciprofloxacin. Organisms resistant to these antibiotics may be susceptible to ciprofloxacin.

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

Pharmacodynamics

In vitro susceptibility data

Breakpoints separate susceptible strains from strains with intermediate susceptibility and the latter from resistant strains:

EUCAST clinical MIC breakpoints [mg/L] or disk diffusion assay values [mm][1] for ciprofloxacin (version 3.1, www. escmid.org).

Species	Susceptible [mg/L] [mm]	Resistant [mg/L] [mm]
Enterobacteriaceae	≤0.5 ≥22	>1 <19
Pseudomonas spp.	≤0.5 ≥25	>1 <22
Acinetobacter spp.	≤1 ≥21	>1 <21
Staphylococcus spp.[2]	≤1 ≥20	>1 <20
S. pneumoniae[3]	≤0.12 ≥50	≥2 <18
H. influenzae[4]	≤0.5 ≥26	>0.5 <26
M. catarrhalis[4]	≤0.5 ≥23	>0.5 <23
N. gonorrhoeae	≤0.032	>0.064
N. meningitidis[5]	≤0.03	>0.06

Non-species-related breakpoints[6, 7]	≤0.5	>1

[1] 5 µg ciprofloxacin disk

[2] *Staphylococcus* spp. breakpoints for ciprofloxacin relate to high-dose therapy.

[3] Wild-type *S. Pneumoniae* is not regarded as susceptible to ciprofloxacin and is therefore classified as intermediate.

[4] Strains with an MIC above the S/I breakpoint (S/I: Susceptible/Intermediary) have not or very rarely been described to date. The identification and determination of antimicrobial susceptibility of such isolates must be repeated; if the results are confirmed, the sample should be submitted to a reference laboratory. These strains should be considered resistant until MIC values over the above-mentioned breakpoints are proven to be antimicrobially effective. “Low-level” resistance to fluoroquinolones (ciprofloxacin MIC of 0.125-0.5 mg/L) can sometimes occur in *Haemophilus influenzae*. There is no evidence to suggest that this "low-level" resistance is of any clinical significance in respiratory infections with *H. influenzae*.

[5] Breakpoints apply only to the prophylaxis of diseases caused by meningococci

[6] “Non-species-related breakpoints” have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of the MIC distribution of specific species. They apply only to species that have no species-specific breakpoint and do not apply to species where interpretation criteria are yet to be determined (Gram-negative anaerobes).

[7] Breakpoints apply to oral doses of 2× 500 mg (or 2× 250 mg for simple urinary tract infections) up to 2× 750 mg and to parenteral doses from 2× 400 mg to 3× 400 mg.

Microbiological susceptibility

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. If 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.

Commonly susceptible species (in vitro)

Aerobic Gram-positive micro-organisms

Bacillus anthracis

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 showing varying susceptibility to ciprofloxacin

Acinetobacter baumannii

Burkholderia cepacia

Campylobacter spp.

Citrobacter freundii

Enterococcus faecalis

Enterobacter aerogenes

Enterobacter cloacae

Escherichia coli

Klebsiella pneumoniae

Klebsiella oxytoca

Morganella morganii

Neisseria gonorrhoeae

Proteus mirabilis

Proteus vulgaris

Providencia spp.

Pseudomonas aeruginosa

Pseudomonas fluorescens

Serratia marcescens

Staphylococcus aureus (methicillin-sensitive)

Staphylococcus saprophyticus
Streptococcus spp.
Peptostreptococcus spp.
Propionibacterium acnes

Inherently resistant species
Staphylococcus aureus (methicillin-resistant)
Stenotrophomonas maltophilia
Actinomyces
Enterococcus faecium
Listeria monocytogenes
Mycoplasma genitalium
Ureaplasma urealyticum
Anaerobic microorganisms, except *Mobiluncus, Peptostreptococcus, Propionibacterium acnes*

Ciprofloxacin in anthrax
The recommended dose for the treatment of anthrax is based mainly on *in vitro* susceptibility data and data from animal studies, as well as on limited data from humans. A 60-day course of treatment with 500 mg ciprofloxacin twice daily is considered to be effective in preventing infection. The attending physician is requested to follow national and/or international guidelines for the treatment of anthrax.
In adults and children after administration of recommended ciprofloxacin doses, mean plasma levels were reached which were the same or above those measured in rhesus monkeys which had inhaled anthrax spores and were subsequently treated with ciprofloxacin. The difference in the mortality of the animals treated with ciprofloxacin versus the untreated control group was statistically significantly in favour of the treated animals ($p = 0.001$).
The pharmacokinetics of ciprofloxacin in humans has been widely studied (see also section “Pharmacokinetics”).
Tolerability data after long-term administration in children, including effects on cartilage tissue, are available only to a very limited extent (see section “Undesirable effects”).
In a placebo-controlled study, rhesus monkeys were exposed to an inhaled dose of anthrax spores equivalent, on average, to 11 times higher than the LD_{50} (about 5.5 × 105, range 5-30 LD_{50}). The minimum inhibitory concentration (MIC 90) for the *B. anthracis* strain used had been determined at 0.08 µg/mL. After oral administration of 125 mg ciprofloxacin at 12-hour intervals for 30 days, peak serum levels of 0.98 µg/mL to 1.69 µg/mL were reached both at T_{max} (1 hour after dosing) and at steady state. Mean serum levels 12 hours after ingestion, known as "trough" levels, were between 0.12 and 0.19 µg/mL. Therapy was initiated 24 hours after exposure to anthrax spores. Mortality in

the animals treated orally for 30 days with ciprofloxacin was significantly lower (1/9 animals) than in the placebo group (9/10 animals). The difference was highly significant (p = 0.001). One of the animals treated with ciprofloxacin died upon completion of the 30-day treatment.

Pharmacokinetics

In *adults,* peak serum levels of 2.97 µg/mL and 4.56 µg/mL, respectively, were measured at steady state after oral administration of 500 mg ciprofloxacin every 12 hours and after intravenous administration of 400 mg every 12 hours. In both cases, the so-called trough levels were determined, on average, to be 0.2 µg/mL at steady state 12 hours after the last administration.
In 10 children aged 6 to 16 years, peak serum concentrations of 8.3 µg/mL were reached after two infusions of 10 mg/kg over 30 minutes at 12-hour intervals; trough concentrations varied between 0.09 and 0.26 µg/mL. Subsequently, the children took ciprofloxacin at a dose of 15 mg/kg. After the first oral dose, mean peak levels of 3.6 µg/mL were measured. Long-term safety data, including data regarding effects on joints and/or surrounding tissue, after ingestion of ciprofloxacin are limited; see also section “Warnings and precautions”.

Absorption

After oral administration, ciprofloxacin is rapidly and almost completely absorbed. Due to the first-pass effect, oral bioavailability is 70-80%. Peak concentrations are reached in blood as early as 60-120 minutes after oral ingestion. Single doses of 100-750 mg produce peak serum concentrations between 0.56 and 3.7 mg/L. The peak concentration in serum (C_{max}) and the serum concentration-time curve (AUC) rise with increasing dose.
Concomitant ingestion of ciprofloxacin with milk or dairy products may cause a reduction in bioavailability by up to 30-36%.

Distribution

At infection sites, i.e. in bodily fluids and tissues, ciprofloxacin is present at concentrations several times higher than in serum. For ciprofloxacin, the volume of distribution at steady state is 2-3 L/kg. As the protein binding of ciprofloxacin is low (20-30%) and the substance is present in blood plasma mainly in non-ionised form, virtually the entire amount of the applied dose diffuses freely into the extravascular space. Thus, concentrations in certain bodily fluids and tissues may considerably exceed the corresponding serum levels.
Only low concentrations of ciprofloxacin reach the cerebrospinal fluid; the peak concentration is around 6-10% that of serum.
After oral or intravenous administration, ciprofloxacin concentrations in bile are several times higher than in serum. Also in prostate tissue and prostate fluid, the ciprofloxacin concentration after oral administration is higher than in serum.

Metabolism/elimination

The mean serum half-life is approximately 4 hours. Renal excretion after a single oral dose is approximately 56%. After intravenous infusion, 71% of the administered dose is excreted with the urine and a further 17.8% with the faeces. Non-renal excretion of ciprofloxacin mainly takes place by active transintestinal secretion, as well as by metabolism. Approximately 10-20% of a single dose (oral or parenteral) is excreted as metabolites. The amounts of individual metabolites recovered are listed below:

Excretion (as % of the ciprofloxacin dose)				
	Oral use		Intravenous use	
Substance	Urine	Faeces	Urine	Faeces
Ciprofloxacin	44.7	25.0	61.5	15.2
Desethylenciprofloxacin	1.4	0.5	1.3	0.5
Sulphociprofloxacin	3.7	5.9	2.6	1.3
Oxociprofloxacin	6.2	1.1	5.6	0.8
Total	56.0	32.5	71.0	17.8

A fourth degradation product (formylciprofloxacin) was found only in a few samples at a rate of less than 0.1%.

Three out of the four ciprofloxacin metabolites show an antibacterial activity comparable or inferior to that of nalidixic acid. The quantitatively smallest metabolite (formylciprofloxacin) is also the most active and its efficacy is largely equivalent to that of norfloxacin.

More than 90% of renal excretion occurs in the first 24 hours. A comparison of the pharmacokinetic parameters of a two-month and three-month intravenous administration did not indicate any accumulation of ciprofloxacin and its metabolites.

Kinetics of special patient groups

Elderly patients

In elderly patients, creatinine clearance should be checked, as the elimination half-life may be prolonged.

Kinetics in patients with impaired renal function:

- Adults:
  In cases of impaired renal function (creatinine clearance <20 mL/min), the dose should be halved or the dosing interval doubled.
- Children:
  Paediatric patients with a renal function less than 50 mL/min creatinine clearance were excluded from the study in children with complicated urinary tract infections and

pyelonephritis. No data are available on dose adjustments in children with moderate to severe renal insufficiency.

Kinetics in patients with impaired hepatic function:

Due to the low metabolic rate of ciprofloxacin, accumulation is unlikely in patients with impaired liver function.

Kinetics in children:

Only limited data are available on the pharmacokinetics in paediatric patients. In a study with children suffering from cystic fibrosis (above one year of age), C_{max} and AUC were not found to be age-dependent. Clearance was higher than in adults (without cystic fibrosis) and the dose used in the study was considerably higher (calculated on an mg/kg basis) than that used in adults. No relevant increase in C_{max} and AUC was observed upon multiple dosing (10 mg/kg 3 times daily). After a 1-hour intravenous infusion of 10 mg/kg in 10 children aged less than 1 year with severe sepsis, C_{max} was 6.1 mg/L (range 4.6-8.3 mg/L), while in contrast, C_{max} was 7.2 mg/L (range 4.7-11.8 mg/L) in children aged 1-5 years. The AUC values in these age groups 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). These values are within the range established in adults at therapeutic doses. Based on population pharmacokinetic analysis in paediatric patients with various infections, a half-life of around 4-5 hours has been calculated and bioavailability of the oral suspension is about 50 to 80%.

Preclinical data

Acute toxicity

The acute toxicity of ciprofloxacin can be regarded as very low. After intravenous infusion, the LD_{50} was 125-290 mg/kg and 2,500-5,000 mg/kg upon oral administration, depending on the animal species.

Chronic toxicity (studies over 6 months)

Oral

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

Parenteral

In the highest dose group (20 mg/kg), slightly elevated urea and creatinine concentrations were recorded in monkeys, as well as changes in the distal renal tubules.

Carcinogenicity and mutagenicity studies

In carcinogenicity studies in mice (21 months) and rats (24 months) at doses up to 1,000 mg/kg body weight per day in mice and 125 mg/kg body weight per day in rats (escalation to 250 mg/kg

body weight per day after 22 weeks), there were no indications of a carcinogenic effect in any dose group.

The results of the *in vitro* and *in vivo* mutagenicity studies revealed no suspicions of any mutagenic effect for ciprofloxacin. This assessment is consistent with the negative results of the carcinogenicity studies on rats and mice.

Reproductive toxicity studies

Ciprofloxacin did not affect fertility performance, intrauterine development and postnatal development in the pups (rats) or fertility performance in the F1 generation. There was no evidence of embryotoxic or teratogenic effects due to ciprofloxacin. There were no effects observed on the peri- and postnatal development of the animals. At the end of the rearing period, no histological damage was detectable at the joints of juvenile animals.

Specific tolerability studies: Studies on articular tolerability

As is known from other gyrase inhibitors, ciprofloxacin causes damage to the large weight-bearing joints of juvenile animals. The extent of the cartilage damage caused is age-, species- and dose-dependent; articular damage can be reduced considerably by taking the weight off the joints. Studies with mature animals (rat, dog) found no indications of any cartilage lesions.

In a study with young beagle dogs after two weeks of treatment at doses 1.3 to 3.5 times higher than the therapeutic dose, ciprofloxacin caused severe articular damage which was still being found even 5 months later.

Further remarks

Influence on diagnostic methods

The *in vitro* activity of ciprofloxacin against *Mycobacterium tuberculosis* might lead to false-negative bacteriological results in samples from patients currently taking ciprofloxacin.

Shelf life

This medicinal product may only be used up to the date marked with “EXP” on the container.

Special storage conditions

Do not store above 30°C. Keep out of the reach of children.

Presentation

Bactiflox 250 Lactab: Packs of 10 and 20 (A)

Bactiflox 500 Lactab: Packs of 10 and 20 (A)

Bactiflox 750 Lactab: Packs of 20 (A)

Marketing authorisation holder

Acino Pharma AG, Liesberg.

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