SELECT THE REQUIRED INFORMATION

PROFESSIONAL INFORMATION

PATIENT INFORMATION LEAFLET

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPROBAY XR 500 500 mg modified-release film-coated tablet
CIPROBAY XR 1000 1 000 mg modified-release film-coated tablet

2. QUALTITATIVE AND QUANTITATIVE COMPOSTION

CIPROBAY XR 500
1 modified-release film-coated tablet contains ciprofloxacin hydrochloride monohydrate and ciprofloxacin hydrated, equivalent to 500 mg ciprofloxacin.
Excipients with known effect: None
Sugar free.

CIPROBAY XR 1000
1 modified-release film-coated tablet contains ciprofloxacin hydrochloride monohydrate and ciprofloxacin hydrated, equivalent to 1000 mg ciprofloxacin.
Excipients with known effect: None
Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CIPROBAY XR 500
Modified-release film-coated tablet.

Nearly white to slightly yellowish coated oblong tablet with C 500 QD imprinted on the upper side and BAYER on the lower side.

CIPROBAY XR 1000
Modified-release film-coated tablet.

Nearly white to slightly yellowish coated oblong tablet with C 1000 QD imprinted on the upper side and BAYER on the lower side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CIPROBAY XR is indicated for the treatment of severe and/or complicated infections caused by ciprofloxacin-sensitive bacteria where other antimicrobials, approved for a similar indication and to which the causative bacteria are sensitive, were considered not to be an appropriate treatment option, have failed, are contraindicated, or not tolerated.
CIPROBAY XR is not indicated/approved for the initiation of treatment (first-line treatment) of infections described as mild/moderate/acute and uncomplicated, caused by bacteria sensitive to ciprofloxacin, unless treatment with other appropriate antimicrobials, approved for a similar

indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated.

CIPROBAY XR 500 is indicated solely for the treatment of:

- Uncomplicated urinary tract infections (acute cystitis) caused by *Escherichia coli* where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated.

CIPROBAY XR 1000 is indicated for the treatment of:

- Severe and/or complicated urinary tract infections caused by *Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, Proteus mirabilis.*
- Acute Uncomplicated Pyelonephritis caused by *Escherichia coli* where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated.
- Severe and/or complicated bacterial diarrhoea caused by *Escherichia coli, Salmonella spp., Shigella spp.*

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to CIPROBAY XR. Therapy with CIPROBAY XR may be initiated in severe and/or complicated infections before results of these tests are known; once results become available, appropriate therapy should be continued.

4.2. Posology and method of administration

Posology

CIPROBAY XR tablets should not be crushed or divided for intake and should be swallowed whole with plenty of liquid with or without meals.

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

CIPROBAY XR 500
In acute uncomplicated urinary tract infections (acute cystitis) where treatment with other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 500 mg once daily for 3 days

CIPROBAY XR 1000
In severe and/or complicated urinary tract infections or acute uncomplicated pyelonephritis where other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 1 000 mg once daily for 7 - 14 days.
In severe and/or complicated bacterial diarrhoea where other appropriate antimicrobials approved for a similar indication and to which the causative bacteria are sensitive, have failed, are contraindicated, or not tolerated: 1 000 mg once daily for up to 7 days.

Missed dose
If a dose is missed, it should be taken anytime but not later than 8 hours prior to the next scheduled dose. If less than 8 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.

Special populations

Geriatric patients (> 65 years)
Elderly patients should receive a dose as low as possible depending on the severity of their illness and on the creatinine clearance (see Patients with renal and hepatic impairment under section 4.2).

Patients with renal and hepatic impairment

Patients with renal impairment
CIPROBAY XR 500
No dose adjustment is required for patients with mild to severe renal impairment (i.e. where creatinine clearance is equal or is less than 30 mL /min/1,73m² or where the serum creatinine concentration is equal or higher than 0,17 mmol/L (2,0 mg/100 mL) including patients on renal dialysis or for patients with impaired liver function**.**
CIPROBAY XR 1000
- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/100 mL), no dose adjustment is required.
- For patients with creatinine clearance is equal to or is less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL) the maximum daily dose should be one CIPROBAY XR 500 tablet. The use of CIPROBAY XR 1000 tablets is not recommended in this patient population.

Patients with renal impairment on haemodialysis:
- For patients with creatinine clearance less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL), the maximum daily dose should be one CIPROBAY XR 500 tablet on dialysis days after dialysis. The use of CIPROBAY XR 1000 tablets is not recommended in this patient population.

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD):
- The maximum daily dose should be one CIPROBAY XR 500 tablet.

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

Patients with renal and hepatic impairment:
- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/100 mL), no dose adjustment is required.
- For patients with creatinine clearance less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL) the maximum daily dose should be one CIPROBAY XR 500 tablet. The use of CIPROBAY XR 1000 is not recommended in this patient population.

Paediatric population

CIPROBAY XR is contraindicated in children less than 18 years of age.
Safety and effectiveness of CIPROBAY XR 500 or CIPROBAY XR 1000 in paediatric patients and adolescents less than 18 years of age have not been established (see sections 4.3 and 4.4).

Method of administration

CIPROBAY XR tablets are to be swallowed whole with a small amount of fluid. CIPROBAY XR tablets must not be crushed, divided or chewed for intake.
CIPROBAY XR 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 XR tablets should

not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, calcium-fortified orange juice). However, dietary calcium as part of a meal does not significantly affect ciprofloxacin absorption.
If the patient is unable to take CIPROBAY XR tablets, because of the severity of the illness or for other reasons (e.g. patients on parenteral nutrition), it is recommended to commence the therapy with an intravenous form of ciprofloxacin. After intravenous administration, the treatment can be continued orally.

4.3. Contraindications

CIPROBAY XR is contraindicated in:

- Patients who have shown hypersensitivity to ciprofloxacin or any other quinolones, or to any of the excipients.
- Pregnancy and lactation (see section 4.6)
- Concomitant use of ciprofloxacin and tizanidine-containing medicines (see section 4.5).
- Concomitant use of ciprofloxacin with other medicines known to prolong the QT interval, or in patients with disorders that prolong the QT interval to such an extent that it leads to prolonged QTcF interval known to associated with serious and potentially fatal dysrhythmias or if symptomatic dysrhythmias occur with concomitant use at time intervals shorter than QT intervals usually associated with dysrhythmias.
- A history of tendon, muscle, joint, central nervous system, epilepsy or psychotic disorders especially those related to previous quinolone/fluoroquinolone use where alternative, appropriate antibiotic choices are available for treatment.
- Myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients.
- Aortic aneurysm and/or dissection or in patients with risk factors or conditions predisposing for aortic aneurysm and/or dissection if alternative appropriate antibiotic choices are available.
- Concomitant use of fluoroquinolones with ACE inhibitors/angiotensin-receptor blockers in patients with moderate to severe renal impairment and in the elderly.
- Patients with confirmed mitral valve and/or aortic valve regurgitation unless no safer appropriate alternative antibiotic is available, has failed, or is not well tolerated.

CIPROBAY XR is contraindicated in children under 18 years. There is evidence of damage to the cartilage of weight bearing joints in immature animals.

4.4. Special warnings and precautions for use

Crystalluria related to the use of ciprofloxacin has been observed. Patients receiving **CIPROBAY XR** should be well hydrated and excessive alkalinity of the urine should be avoided.

Side-effects that may be potentially life-threatening are pancytopenia and marrow depression (see section 4.8).

Concurrent administration with methotrexate may increase the concentration of methotrexate to toxic levels.

Tendinitis may occur. It most frequently involves the Achilles tendon and may lead to tendon rupture. The risk of tendinitis and tendon rupture is increased in the elderly and in patients using corticosteroids. Close monitoring of these patients is therefore necessary if CIPROBAY XR is prescribed. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with CIPROBAY XR must be discontinued immediately, and appropriate treatment (e.g. immobilisation) must be initiated for the affected tendon.

Tendinitis and/or tendon rupture may still occur for several months after completion of treatment. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Children and adolescents
CIPROBAY XR is contraindicated in patients less than 18 years (see section 4.3). In children, arthropathy is reported to occur commonly (see Paediatric population under section 4.2).

Cardiac disorders
CIPROBAY XR has been associated with QT prolongation (see sections 4.3 and 4.8). Women tend to have a longer baseline QTc interval compared with men and may be more sensitive to medicines prolonging the QT interval, such as CIPROBAY XR.
Elderly patients may also be more susceptible to effects of CIPROBAY XR on the QT interval.
Concomitant use of CIPROBAY XR with medicines or in patients with disorders that can result in prolongation of the QT interval is contraindicated if concomitant use leads to prolongation of QTc interval associated with serious or potentially fatal dysrhythmias or symptomatic dysrhythmias occur at QTc intervals less than usually associated with dysrythmias (see section 4.3) e.g., class IA or III antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics, (see section 4.5*) or* congenital long QT syndrome, risk of Torsades de Pointes, uncorrected electrolyte imbalance such as hypokalaemia or hypomagnesaemia and cardiac disease such as heart failure, myocardial infarction, or bradycardia. A pre-treatment ECG and frequent follow up ECG monitoring is mandatory with concomitant use to determine whether concomitant use is contraindicated.
There is some evidence of an increased risk of aortic aneurysm and dissection after intake of fluoroquinolones, particularly in the elderly 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 aneurysmal disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissections, or in the presence of other risk factors or conditions predisposing aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known arthrosclerosis) (see section 4.3).
In case of sudden abdominal, chest, or back pain, patients should be advised to immediately consult a medical practitioner in an emergency department of a hospital.
Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury in patients, especially those with moderate to severe renal impairment and elderly patients (see section 4.3). Renal function should be assessed before initiating treatment, and monitored during treatment, with fluoroquinolone and ACE inhibitors/angiotensin receptor blockers.
There is some evidence, although inconclusive, of a possible association between fluoroquinolone use and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed.
Fluoroquinolones should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see section 4.3).

Cytochrome P450
Ciprofloxacin is known to be a moderate inhibitor of the CYP 450 1A2 enzymes. Care should be taken when other medicines are administered concomitantly which are metabolised via the same enzymatic pathway (e.g. theophylline, methylxanthines, caffeine, duloxetine, ropinirole, clozapine, olanzapine, agomelatine). Increased plasma concentrations associated with specific side effects may be observed due to inhibition of their metabolic clearance by ciprofloxacin (see section 4.5).

Gastrointestinal System
Pseudomembranous colitis which may be fatal if not treated should be considered if severe and persistent diarrhoea develop during and after treatment with CIPROBAY XR.

In such cases CIPROBAY XR must be discontinued and appropriate antimicrobial and supportive therapy should be initiated. Medicines that inhibit peristalsis are contraindicated in this situation.

Hepatobilliary system
Cases of hepatic necrosis and life-threatening hepatic failure have been reported with CIPROBAY XR. In the event of any signs and symptoms of hepatic disease (such as anorexia, jaundice, dark urine, pruritus, or tender abdomen), treatment should be discontinued (see section 4.8).
There may be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage (see section 4.8).

Seizures
CIPROBAY XR is known to trigger seizures or lower the seizure threshold.
In epileptic patients who have suffered from previous central nervous system (CNS) disorders (e.g. lowered convulsion threshold, previous history of convulsions, reduced cerebral blood flow, altered brain structure or stroke). CIPROBAY XR should only be used where alternative appropriate therapies have failed, are contraindicated, or not tolerated, since these patients are endangered due to possible central-nervous system side effects. Cases of status epilepticus have been reported (see sections 4.3 and 4.8). If seizures occur, CIPROBAY XR should be discontinued.

Peripheral neuropathy
Cases of sensory or sensorimotor polyneuropathy resulting in paraesthesias, hypoaesthesias, dysaesthesias, or weakness have been reported in patients receiving fluoroquinolones including CIPROBAY XR. Patients on treatment with CIPROBAY XR should be advised to inform their medical practitioner prior to continuing treatment if symptoms of neuropathy such as pain, burning, tingling, numbness, or weakness develop (see section 4.8). The recovery process of neuropathies may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.

Psychiatric reactions
Psychiatric reactions may occur after the first administration of fluoroquinolones, including CIPROBAY XR. Cases of depression or psychotic reactions may progress to suicidal ideations/thoughts and self-injury, such as attempted or completed suicide (see sections 4.3 and 4.8). In the event that the patient develops these reactions, CIPROBAY XR should be discontinued and appropriate measures instituted.

Hypersensitivity
Hypersensitivity and allergic reactions, including life-threatening anaphylactic/anaphylactoid shock may occur with the first exposure to CIPROBAY XR. In these cases, CIPROBAY XR must be discontinued~~,~~ and appropriate medical treatment instituted.

Myasthenia gravis
The use of CIPROBAY XR in patients with myasthenia gravis is contraindicated if alternative appropriate antibiotic choices are available (see section 4.3). CIPROBAY XR may exacerbate the symptoms of myasthenia gravis.

Tendinitis and tendon rupture
Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with CIPROBAY XR, even within the first 48 hours of treatment. Cases occurring up to several months after completion of therapy have been reported (see sections 4.3 and 4.8). The risk of tendinopathy may be increased in elderly patients, during strenuous physical activity, in patients treated concomitantly with corticosteroids, in patients with renal impairment and patients with solid organ transplants.
At any sign of tendinitis (e. g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the

administration of CIPROBAY XR should be discontinued. The recovery process may be prolonged (weeks to months) and full recovery to the pre-treatment status may not occur.
CIPROBAY XR should not be used in patients with a history of tendon disorders, especially those related to previous exposure to quinolone or fluoroquinolone use (see section 4.3).

Skin and Appendages
CIPROBAY XR has been shown to produce photosensitivity reactions. Patients taking CIPROBAY XR should avoid direct exposure to excessive sunlight or UV-light. Therapy should be discontinued if photosensitisation (i.e. sunburn-like skin reactions) occurs (see section 4.8).

Dysglycaemia
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with CIPROBAY XR. In CIPROBAY-XR treated patients, dysglycaemia occurred predominantly in elderly diabetic patients receiving concomitant treatment with an oral hypoglycaemic agent (e.g. sulfonylurea) or with insulin. In diabetic patients, careful monitoring of blood glucose is recommended (see section 4.8).

Interaction with laboratory tests
Ciprofloxacin may interfere with the *Mycobacterium tuberculosis* culture test by suppression of mycobacterial growth, causing false negative results in specimens from patients currently taking CIPROBAY XR.

Influence on laboratory parameters / urinary sediment
CIPROBAY XR may cause a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, or a temporary increase in urea, creatinine or bilirubin in the serum. Hyperglycaemia, hypoglycaemia, crystalluria or haematuria may occur.

Renal impairment
Patients with severe renal impairment (creatinine clearance less than 30 mL/min/1,73m² or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/100 mL) should receive CIPROBAY XR 500 per day and should not receive CIPROBAY XR 1000 tablets (see Patients with renal and hepatic impairment ~~in~~ under section 4.2).

4.5. Interaction with other medicines and other forms of interactions

Medicines known to prolong QT interval
CIPROBAY XR should not be used in patients receiving medicines known to prolong the QT interval (e.g. Class IA and II antidysrhythmics, tricyclic antidepressants, macrolides, antipsychotics) (see sections 4.3 and 4.4).

Chelation Complex Formation
The simultaneous administration of CIPROBAY XR and multivalent cation-containing medicines and mineral supplements (e.g. calcium, magnesium, aluminium, iron), polymeric phosphate binders (e.g. sevelamer, lanthanum carbonate), sucralfate or antacids and highly buffered medicines (e.g. anti-retrovirals)~~,~~ containing magnesium, aluminium or calcium reduce the absorption of CIPROBAY XR. Consequently, CIPROBAY XR 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 XR should be avoided because the absorption of CIPROBAY XR is reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

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

Omeprazole
Concomitant administration of CIPROBAY XR and omeprazole-containing medicines results in a 20 % reduction of the C_{max} and AUC of CIPROBAY XR.

Theophylline
Concurrent administration of CIPROBAY XR with theophylline-containing medicines may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related side effects. If concomitant use of the two medicines cannot be avoided, plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate (see Cytochrome P450 under section 4.4).

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 under section 4.4). Tizanidine-containing medicines must not be administered together with Ciprobay XR (see section 4.3).

Other xanthine derivatives
Concurrent administration of CIPROBAY XR with caffeine or pentoxifylline (oxpentifylline) containing products, may lead to raised serum concentrations of these xanthine derivatives.

Phenytoin
Altered (decreased or increased) serum levels of phenytoin were observed in patients receiving CIPROBAY XR and phenytoin simultaneously. To avoid the loss of seizure control associated with decreased phenytoin levels, and to prevent phenytoin overdose-related side effects when CIPROBAY XR is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum concentration measurements, is recommended during and shortly after co-administration of CIPROBAY XR with phenytoin.

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

NSAID
Concomitant administration of the nonsteroidal anti-inflammatory drugs with quinolones such as CIPROBAY XR increases the risk of central nervous system stimulation and seizures.

Ciclosporin
Monitoring of serum creatinine concentrations is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed.

Vitamin K antagonists
Simultaneous administration of CIPROBAY XR with warfarin may augment its anticoagulant effects. The INR should be monitored frequently during and shortly after co-administration of CIPROBAY XR with warfarin.

Duloxetine
An increase of duloxetine blood concentrations can be expected upon concomitant administration with CIPROBAY XR (see Cytochrome P450 ~~in~~ under section 4.4)

Ropinirole
Concomitant use of ropinirole with ciprofloxacin, as contained in CIPROBAY XR, a moderate inhibitor of the CYP450 1A2 isozyme, resulted in an increase of C_{max} and AUC of ropinirole by 60 % and 84 %, respectively. Monitoring ropinirole-related side effects, dose adjustments as appropriate is recommended during and shortly after co-administration with CIPROBAY XR (see section 4.4).

Lidocaine (Lignocaine)
Concomitant use of lidocaine (lignocaine)-containing medicines with ciprofloxacin, a moderate inhibitor of CYP450 1A2 isozyme, reduces the clearance of intravenous lidocaine by 22 % and may increase the risk for lidocaine side effects.

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 XR are advised (see section 4.4).

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 is advised when prescribing CIPROBAY XR concomitantly with sildenafil.

ACE inhibitors and angiotensin-receptor blockers
Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury in patients with moderate to severe renal impairment and the elderly (see section 4.3).

Agomelatine
In clinical studies, it was demonstrated that fluvoxamine, as a strong inhibitor of the CYP450 1A2 isoenzyme, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no clinical data are available for a possible interaction with ciprofloxacin, a moderate inhibitor of CYP450 1A2, similar effects can be expected upon concomitant administration (see 'Cytochrome P450' in section 4.4).

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

4.6. Pregnancy and lactation

Safety of CIPROBAY XR during pregnancy and lactation has not been established.

Pregnancy
The safety of CIPROBAY XR in pregnant women has not been established. CIPROBAY XR must not be prescribed to pregnant women. Animal studies demonstrated that ciprofloxacin may damage the articular cartilage in the foetus.

Breastfeeding

Ciprofloxacin is excreted in breast milk. Due to the potential risk of articular damage, mothers on CIPROBAY XR should not breastfeed their infants.

4.7. Effects on ability to drive and use machines

CIPROBAY XR may result in an impairment of the patient's ability to drive or operate machinery due to musculoskeletal and/or CNS reactions (see section 4.8).

4.8. Undesirable effects

Tabulated list of adverse reactions
The frequencies of side effects reported with ciprofloxacin in all clinical studies are summarised in the table below.
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000).

System Organ Class	Common	Uncommon	Rare	Very Rare
Infections and Infestations		Mycotic superinfections	Antibiotic associated colitis/ pseudomembranous colitis (with possible fatal outcome)	
Blood and Lymphatic System Disorders		Eosinophilia	Leukopenia Anaemia Neutropenia Leukocytosis Thrombocytopenia Thrombocytaemia	Haemolytic anaemia Agranulocytosis Life-threatening pancytopenia Life-threatening bone marrow depression
Immune System Disorders			Allergic reaction Allergic oedema / angiooedema	Anaphylactic reaction Life-threatening anaphylactic shock Serum sickness-like reaction
Metabolism and Nutrition Disorders		Decreased appetite and food intake	Hyperglycaemia Hypoglycaemia, particularly in diabetic patients	
Psychiatric Disorders		Psychomotor hyperactivity / agitation	Confusion and disorientation Anxiety reaction Abnormal dreams Depression (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour, such as suicidal ideations/ thoughts and attempted or completed suicide)

System Organ Class	Common	Uncommon	Rare	Very Rare
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Par- and Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperaesthesia Intracranial hypertension (pseudotumuor cerebri)
Eye Disorders			Visual disturbances	Visual colour distortions
Ear and Labyrinth Disorders			Tinnitus Hearing loss	Impaired hearing
Cardiac Disorders			Tachycardia	
Vascular Disorders			Vasodilatation Hypotension Syncope	Vasculitis
Respiratory, Thoracic and Mediastinal Disorders			Dyspnoea (including asthma)	
Gastrointestinal Disorders	Nausea Diarrhoea	Vomiting Gastrointestinal and abdominal pains Dyspepsia Flatulence		Pancreatitis
Hepatobiliary Disorders		Increase in transaminases Increased bilirubin	Hepatic impairment Jaundice Non infective hepatitis	Liver necrosis (which may progress to life-threatening hepatic failure)
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome Toxic epidermal necrolysis
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendinitis Tendon rupture (predominantly Achilles tendon) Exacerbation of symptoms of myasthenia gravis
Renal and Urinary Disorders		Renal impairment	Renal failure Haematuria Crystalluria Tubulointerstitial nephritis	
General Disorders and Administration Site Conditions		Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance

System Organ Class	Common	Uncommon	Rare	Very Rare
Investigations		Increase in blood alkaline phosphatase	Abnormal prothrombin level (increased INR) Increased amylase	

The following side effects have been reported from post marketing surveillance and frequency could not be estimated.
Metabolism and Nutrition Disorders: Hyperglycaemia, hypoglycaemic coma
Nervous System Disorders: Peripheral neuropathy and polyneuropathy and Guillain-Barre syndrome
Cardiac Disorders: QT prolongation, ventricular dysrhythmia, Torsades de Pointes *, aortic aneurysm and dissection
Skin and subcutaneous tissue disorders: Acute generalised exanthematous pustulosis (AGEP)
Investigations: Increased International normalised ratio (INR) (in patients treated with Vitamin K antagonists)
*These events were reported during the post-marketing period (see section 4.4).

Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones. Due to insufficient post-marketing information in the reported cases, it is unknown whether fluoroquinolone use was the causative factor, or a contributory factor, or played no role in the reported cases where mitral and/or aortic valve regurgitation was diagnosed.

In isolated instances, some serious adverse reactions may be long-lasting (> 30 days) and disabling; such as tendinitis, tendon rupture, musculoskeletal disorders, and other reactions affecting the nervous system including psychiatric disorders and disturbance of senses.

In clinical studies the following side effects had 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, paraesthesia and dysaesthesia, seizures, vertigo, visual disturbances, hearing loss, tachycardia, vasodilation, hypotension, transient hepatic impairment, jaundice, renal failure, oedema
Rare:	Pancytopenia, bone marrow depression, anaphylactic shock, psychotic reactions, migraine, smell disorders, hearing impaired, vasculitis, pancreatitis, liver necrosis, petechiae, tendon rupture

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9. Overdose

In overdose, side effects may be exaggerated or exacerbated (see section 4.8).
In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported. Apart from routine emergency measures, it is recommended to monitor renal function, including urinary pH and acidity, if required, to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of ciprofloxacin in overdoses. Only a small quantity of ciprofloxacin (< 10 %) is eliminated by haemodialysis or peritoneal dialysis. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Fluoroquinolones
ATC Code: J01MA02

Ciprofloxacin is a synthetic, 4-quinolone derivative with *in vitro* bactericidal activity against Gram-negative and Gram-positive organisms. Ciprofloxacin has a bactericidal action, not only in the proliferation phase but also in the resting phase. During the proliferation phase of a bacterium a segmental twisting and untwisting of the chromosomes take place. An enzyme called DNA gyrase plays a decisive part in this process. Ciprofloxacin inhibits this DNA gyrase in a way that arrests the bacterial metabolism, since vital information can no longer be read from the bacterial chromosome.
Resistance to ciprofloxacin develops slowly and in stages (multiple-step type).
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 that occurs with β-lactam antibiotics, aminoglycosides, and tetracyclines has not been observed with ciprofloxacin. Plasmid-carrying bacteria are also completely sensitive to ciprofloxacin. Parallel resistance to other important but chemically different, active substance groups, such as β-lactam antibiotics, aminoglycosides, tetracyclines, macrolide or peptide antibiotics, sulphonamides, trimethoprim or nitrofuran derivatives is not seen with ciprofloxacin.
The following microorganisms are considered inherently resistant to ciprofloxacin: *Staphylococcus aureus* (methicillin-resistant) and *Stenotrophomonas maltophilia, Actinomyces, Enteroccus faecium, Listeria monocytogenes, Mycoplasma genitalium, Ureaplasma urealitycum,* anaerobic microorganisms (Except *Mobiluncus, Peptostreptococus, Propionibacterium acnes)*
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information gives only an approximate guidance on probabilities whether microorganisms will be susceptible for ciprofloxacin or not.

5.2. Pharmacokinetic properties

Ciprofloxacin modified release tablets are formulated to release the active medicinal product at a slower rate compared to immediate-release tablets. Approximately 35 % of the dose is contained within an immediate-release component, while the remaining 65 % is contained in a slow-release matrix. Ciprofloxacin tablets are designed to release all of the dose prior to the tablet reaching the distal region of the small intestine. Following oral administration of CIPROBAY XR tablets, ciprofloxacin is almost completely absorbed.
The pharmacokinetics of ciprofloxacin modified release tablets are not altered by the co-administration with food. The elimination kinetics of ciprofloxacin are similar for the immediate-release and the ciprofloxacin modified release tablet. In studies comparing the 500 mg modified release regimen and the 250 mg bd regimen, approximately 35 % of an orally administered dose was excreted in the urine as unchanged drug for both formulations.
The urinary excretion of ciprofloxacin is virtually complete within 24 hours after dosing. The renal clearance of ciprofloxacin, which is approximately 300 mL/minute, exceeds the normal glomerular filtration rate of 120 mL /minute. Thus, active tubular secretion would seem to play a significant role in its elimination.
Although bile concentrations of ciprofloxacin are several folds higher than serum concentrations after oral dosing with the immediate-release tablet, only a small amount of the dose administered is recovered from the bile as unchanged drug. An additional 1 % to 2 % of the dose is recovered from the bile in the form of metabolites. Approximately 20 % to 35 % of an oral dose of immediate-release ciprofloxacin is recovered from the faeces within 5 days after dosing. This may arise from either biliary clearance or transintestinal elimination.

CIPROBAY XR 500

The area under the plasma-concentration time curve (AUC) following a single dose is 7,24 mg*h/L (geo mean). Maximum plasma concentrations of 1,42 mg/L (geo mean) are attained between 1 and 4 hours after dosing.

At steady state the relative bioavailability amounts to approximately 97 % (90 % C.I.: 89 – 107 %). Exposure to drug in terms of AUC at steady state is approximately 7,77 mg*h/L (geo mean). Within 1 to 2,5 hours after ingestion of a 500 mg dose, peak concentrations of approximately 1,54 mg/L (geo mean) are reached during once-daily treatment with CIPROBAY XR. The terminal half-life is approximately 5 hours. The steady state trough ciprofloxacin plasma concentration at the end of the dosing interval ($C_{24,ss}$) is (0,033 mg/L, geo. mean).

No accumulation of the drug is observed at steady state.

Representative single dose and steady state urinary concentrations of ciprofloxacin (mg/L) after once-daily administration of a 0,5 g modified release tablet are presented in the table below (mean range).

Time post dose (Mid-point of the urine collection time interval, collection interval)				
	2 h (0-4 h)	6h (4-8 h)	10 h (8-12 h)	18h (12-24h)
Concentration in mg/L mean (range)				
Single dose	338 (70-896)	137 (26-289)	57 (7,5-174)	27 (12-55)
Steady state	368 (73-968)	166 (30-298)	53 (15-143)	30 (7,7-71)

	C_{max} (mg/L)	AUC_{o-24h}	$T_{1/2}$ (hr)	T_{max}(hr)§
CIPROBAY XR 500 od	1,59 ± 0,43	7,97 ± 1,87	6,6 ± 1,4	1,5 (1-2,5)
Ciprobay 250 bd	1,14 ± 0,23	8,25 ± 2,15	4,8 ± 0,6	1,0 (0,5-2,5)

§ median (range)

CIPROBAY XR 1000

Pharmacokinetic parameters obtained at steady state with the 500 mg twice daily and 1000 mg once-daily dose regimens are shown in the table below. Maximum plasma concentrations are attained between 1 and 4 hours after dosing. C_{max} values obtained with CIPROBAY XR 1000 were higher than seen with the corresponding twice daily regimen, but AUC values for the once-daily and twice daily regimens were equivalent.

Time post dose (Mid-point of the urine collection time interval, collection interval)				
	2 h (0-4 h)	6h (4-8 h)	10 h (8-12 h)	18h (12-24h)
Concentration in mg/L mean (range)				
Single dose	397 (70-1614)	294 (30-1586)	121 (11-581)	58 (8,6-198)
Steady state	589 (108-3030)	359 (26-1991)	160 (36-843)	65 (5,3-204)

	C_{max} (mg/L)	AUC_{o-24h}	$T_{1/2}$ (hr)	T_{max}(hr)§
CIPROBAY XR 1000 od	3,11±1,08	16,83±5,65	6,31 ±0,72	2,0 (1-4)
Ciprobay 500 bd	2,06±0,41	17,04±4,79	5,66 ±0,89	2,0 (0,5-3,5)

§ median (range)

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Crospovidone
Hypromellose 15cP

Magnesium stearate
Polyethylene glycol
Silica colloidal anhydrous
Succinic acid
Titanium dioxide

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

CIPROBAY XR 500: 3 years
CIPROBAY XR 1000: 2 years.

6.4. Special precautions for storage

Store at or below 25 °C.
Store in a dry place.

6.5. Nature and contents of container

- Carton containing a white opaque HDPE plastic bottles with a PP child-resistant screw-cap closure with PE seal; or
- Carton containing PA/Alu/PP/aluminium foil blisters; or
- Carton containing PP/aluminium foil blisters.

CIPROBAY XR 500: Pack size of 3 modified-release film-coated tablets.
CIPROBAY XR 1000: Pack-size of 7 modified-release film-coated tablets.

6.6. Special precautions for disposal

Not applicable.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609

8. REGISTRATION NUMBER

CIPROBAY XR 500: 37/20.1.1/0250
CIPROBAY XR 1000: 38/20.1.1/0024

9. DATE OF FIRST AUTHORISATION

CIPROBAY XR 500: 24 October 2003
CIPROBAY XR 1000: 25 November 2005

10. DATE OF REVISION OF THE TEXT

CIPROBAY XR 500: 11 August 2020
CIPROBAY XR 1000: 11 August 2020