SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPROBAY® 500 500 mg Tablet
CIPROBAY® IV 2 mg/mL Solution for infusion
CIPROBAY® SUSPENSION 5 % Oral Suspension
DILUENT FOR CIPROBAY SUSPENSION 5 % AND 10 % Solution

2. QUALTITATIVE AND QUANTITATIVE COMPOSTION

CIPROBAY tablets
Each film-coated tablet contains 500 mg ciprofloxacin (as hydrochloride).

CIPROBAY IV
Each glass bottle with 50 mL infusion solution contains 100 mg ciprofloxacin. The sodium chloride content is 450 mg (7,7 mmol).
Each glass bottle with 100 mL infusion solution contains 200 mg ciprofloxacin. The sodium chloride content is 900 mg (15,4 mmol).
Each glass bottle with 200 mL infusion solution contains 400 mg ciprofloxacin. The sodium chloride content is 1 800 mg (30,8 mmol).

CIPROBAY SUSPENSION 5 %
5 mL suspension after reconstitution (1 measuring spoon) contains 250 mg ciprofloxacin (as ciprofloxacin hydrated).
2.5 mL suspension after reconstitution (1/2 measuring spoon) contains 125 mg ciprofloxacin (as ciprofloxacin hydrated).
Excipients: Sucrose. One measuring spoon (5 mL of suspension) contains approx. 1,4 g of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

CIPROBAY tablets
Film-coated tablets

500: Oblong, nearly white to slightly yellowish tablets marked with “CIP 500” on one side and “BAYER” on the reverse side.

The tablets can be divided into equal doses.

CIPROBAY IV
Solution for infusion.

Clear, colourless to slightly yellowish solution.

The pH-value of the solution for infusion ranges from 3,9 to 4,5.

CIPROBAY SUSPENSION 5 % and DILUENT FOR CIPROBAY SUSENSION 5 % AND 10 %
Microcapsules and diluent for oral suspension

Appearance before reconstitution:
Microcapsules: white to slightly yellowish granules for reconstitution.
Diluent: White to slightly yellowish, oily suspension with strawberry odour, occasionally may contain yellow-orange droplets and globular particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

CIPROBAY 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 in 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 is indicated for the treatment of the following bacterial infections where these infections are compliant with the indication context.

- **Severe and/or complicated lower respiratory tract infections** caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Pseudomonas aeruginosa, Haemophilus influenza,* and *Haemophilus para-influenzae.*
- **Severe and/or complicated urinary tract infections** caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Providencia rettgeri, Morganella morganii, Citrobacter diversus, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Streptococcus faecalis*.
- **Severe and/or complicated skin and soft tissue infections** caused by *Escherichia coli, Klebsiella pneumoniae, Enterobacter cloacae, Proteus mirabilis, Proteus vulgaris, Providencia stuartii, Morganella morganii, Citrobacter freundii, Pseudomonas aeruginosa, Staphylococcus epidermidis* and *Streptococcus pyogenes.*
- **Severe and/or complicated gastro-intestinal infections:** Infective diarrhoea caused by *Escherichia coli, Campylobacter jejuni, Shigella flexneri* and *Shigella sonnei.*
- **Severe and/or complicated bone infections:** Osteomyelitis due to susceptible Gram-negative organisms.
- **Prophylaxis of invasive infections** due to *Neisseria meningitidis* in patients over 18 years of age.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside must be administered concomitantly.

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. Therapy with CIPROBAY 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 tablets and CIPROBAY SUSPENSION 5 %
The dosage range is 250 - 750 mg twice daily. The duration of treatment to contain and eradicate an infection depends upon the type and severity of the infection, immunological status, clinical response and bacteriological findings. Use the lowest effective dose for the shortest time to contain and eradicate infection.

For infections of the kidneys, urinary tract and abdominal cavity the treatment period is up to 7 days.
In all other infections the treatment period is 7-14 days.
In streptococcal infections, the treatment must last at least 10 days because of the risk of late complications.

Severe and/or complicated infections of the lower respiratory tract: 750 mg twice daily. In cystic fibrosis patients the dose is 750 mg twice daily. The low body mass of these patients should, however, be taken into consideration when determining dosage (7,5 to 15 mg/kg/day).
Severe and/or complicated infections of the urinary tract: 500 mg twice daily.
Severe and/or complicated infections of the skin: 750 mg twice daily.
Severe and/or complicated infectious diarrhoea: 500 mg twice daily.
Severe and/or complicated bone infections: 750 mg twice daily. Treatment may be required for 4 - 6 weeks or longer.
Prophylaxis of invasive infections due to *Neisseria meningitides:* 500 mg single dose tablet or oral suspension**.**

In cases of a mild/moderate/acute and uncomplicated infection, where all other appropriate antimicrobials approved for a similar indication have failed, are contraindicated, or are not well tolerated, the following dosage instruction are advised:
Infections of the lower respiratory tract: 250 mg twice daily
Infections of the urinary tract: 250 mg twice daily
Infections of the skin: 500 mg twice daily
Infectious diarrhoea: 500 mg twice daily
Bone infections: 500 mg twice daily

If the patient is unable to take CIPROBAY film-coated tablets or suspension, because of the severity of the illness or for other reasons (e.g. patients on parenteral nutrition), therapy should be commenced with intravenous CIPROBAY. After intravenous administration treatment may be continued orally.

CIPROBAY IV
The dosage of CIPROBAY IV is determined by the severity and type of infection, the sensitivity of the causative organism(s) and the age, mass and renal function of the patient. The usual dose is 100 mg - 200 mg IV every 12 hours. For severe and/or complicated infections 400 mg may be administered every 12 hours (i.e. bd). Intravenous therapy should be discontinued as soon as oral CIPROBAY therapy can be substituted. The usual duration of intravenous therapy is up to 7 days.

Cystic fibrosis
In cystic fibrosis patients the usual dose is 200 mg IV twice daily. The often low body mass of these patients should, however, be taken into consideration when determining dosage (5 - 10 mg / kg / day).

Missed dose
If a dose is messed, it should be taken anytime but not later than 6 hours prior to the next scheduled dose. If less than 6 hours remains 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 as low a dose as possible; this will depend on the severity of the illness and on the creatinine clearance (see section 4.2 for dose adjustment).

Patients with renal and hepatic impairment
Patients with renal impairment
- Patients with creatinine clearance between 30 and 60 mL/min/1, 73m² (moderate renal impairment) or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration or 800 mg for an intravenous regimen.
- Patients with creatinine clearance less than 30 mL/min/1,73m² (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/dL) the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen.

Patients with renal impairment on haemodialysis
- For patients with creatinine clearance between 30 and 60 mL/min/1,73m² (moderate renal impairment) or serum concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration (all formulations) or 800 mg for an intravenous regimen.
- For patients with creatinine clearance less than 30 mL/min/1,73m² (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/dL), the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen on dialysis days after dialysis.

Patients with renal impairment on continuous ambulatory peritoneal dialysis (CAPD)
- Addition of CIPROBAY solution for infusion to the dialysate (intraperitoneal): 50 mg ciprofloxacin / litre dialysate administered 4 times a day every 6 hours
- The maximum daily oral dose of CIPROBAY should be 500 mg (1 x 500 mg CIPROBAY film-coated 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 (moderate renal impairment) or serum creatinine concentration between 0,12 and 0,16 mmol/L (1,4 and 1,9 mg/dL), the maximum daily dose should be 1 000 mg for oral administration (all formulations) or 800 mg for an intravenous regimen
- For patients with creatinine clearance less than 30 mL/min/1,73m² (severe renal impairment) or serum creatinine concentration equal or higher than 0,17 mmol/L (2,0 mg/dL) the maximum daily dose should be 500 mg for oral administration (all formulations) or 400 mg for an intravenous regimen.

Method of administration

CIPROBAY tablets and suspension can be taken independent of mealtimes.
If CIPROBAY is taken on an empty stomach, the active substance is absorbed more rapidly.

A reduction in absorption of ciprofloxacin can be expected if taken with dairy products or with mineral-fortified drinks. The film-coated tablets or suspension should not be taken concurrently with dairy products or with mineral-fortified drinks alone (e.g. milk, yoghurt, and calcium fortified orange juice). However, dietary calcium as part of a meal does not significantly affect CIPROBAY absorption (see section 4.5).

CIPROBAY tablets
CIPROBAY tablets should be swallowed whole with plenty of liquid.

CIPROBAY SUSPENSION
Always use the graduated measuring spoon to obtain the exact dose:
½ measuring spoonful (approximately 2,5 mL) contains approximately 125 mg ciprofloxacin. 1 measuring spoonful (approximately 5,0 mL) contains approximately 250 mg ciprofloxacin.

For instructions on reconstitution of the product before administration, see section 6.6.

Appearance of the reconstituted product
When reconstituted as directed, the final mixed suspension is white to slightly yellowish with a strawberry odour, occasionally may contain yellow-orange droplets and globular particles.

CIPROBAY IV
CIPROBAY IV should be administered by intravenous infusion over a period of 60 minutes. Slow infusion into a large vein will minimize patient discomfort and reduce the risk of venous irritation. The infusion solution can be infused either directly or after mixing with the other compatible infusion solutions (see section 6.6).

For ease of use the infusion vial stopper should be pierced in the central ring. Piercing of the outer ring may result in the vial stopper being forced into the vial.

4.3. Contraindications

CIPROBAY is contraindicated in:

- patients who have shown hypersensitivity to ciprofloxacin or any other quinolones or to any of the excipients listed in section 6.1.
- 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.
- pregnancy and lactation (see section 4.6)
- myasthenia gravis where alternative appropriate antibiotic choices are available to treat these patients.
- concurrent administration of CIPROBAY and tizanidine (see section 4.5).
- 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.
- 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.
- 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.
- concomitant use of fluoroquinolones with ACE inhibitors/angiotensin-receptor blockers in patients with moderate to severe renal impairment (creatinine clearance ≤ 30 mL/min) and in the elderly.

CIPROBAY 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 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 and in patients with a kidney or lung transplant. Close monitoring of these patients is therefore necessary if CIPROBAY is prescribed. All patients should consult their medical practitioner if they experience symptoms of tendinitis. If tendinitis is suspected, treatment with CIPROBAY 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.

***Streptococcus pneumoniae* infections**
CIPROBAY should not be used for treatment of pneumococcal infections due to limited efficacy against *Streptococcus pneumoniae.*

Severe infections and/or infections due to Gram-positive or anaerobic bacteria
For the treatment of severe infections, CIPROBAY should be used in combination with another appropriate antibacterial medicine.
CIPROBAY should not be used in staphylococcal infections and infections involving anaerobic bacteria.

Cardiac disorders
CIPROBAY 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 QTC interval, such as CIPROBAY.
Elderly patients may be more susceptible to effects of CIPROBAY on the QT interval.
Concomitant use of CIPROBAY 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 dysrhythmias 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).

Children and adolescents
CIPROBAY is contraindicated in children below the age of 18 years (see section 4.3). In children, arthropathy is reported to occur commonly (see additional information on special populations in section 4.2).

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

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.
In such cases CIPROBAY 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. 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).

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

Tendinitis and tendon rupture
Tendinitis and tendon rupture (predominantly Achilles tendon), sometimes bilateral, may occur with CIPROBAY, even within the first 48 hours of treatment. Cases occurring up to several months after completion of therapy have been reported (see 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 administration of CIPROBAY should be discontinued and physical exercise be avoided.

At any sign of tendinitis (e.g. painful swelling, inflammation) the affected extremity should be kept at rest, any inappropriate physical exercise should be avoided, a physician should be consulted and the antibiotic treatment should be discontinued. CIPROBAY 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). CIPROBAY should only be used in these patients if appropriate alternative antibiotic choices are not available, have failed, are contraindicated, or not tolerated.

Seizures
CIPROBAY is known to trigger seizures or lower the seizure threshold.
In patients with epilepsy and in 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 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 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. Patients on treatment with CIPROBAY 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 neuropathy may be prolonged (weeks or 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. 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 a patient develops any of these reactions, CIPROBAY should be discontinued and appropriate measures instituted.

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

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

Dysglycaemia
As with all fluoroquinolones, disturbances in blood glucose, including both hypoglycaemia and hyperglycaemia have been reported with CIPROBAY. In CIPROBAY-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).

Concomitant use with ACE inhibitors/Angiotensin-receptor blockers
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 fluoroquinolones or ACE inhibitors/angiotensin-receptor blockers whether used separately or concomitantly.

Local reactions
Phlebitis or thrombophlebitis, local irritation and pain at the site of injection have been reported with intravenous administration of CIPROBAY (see section 4.8).
Intravenous infusion should be administered by slow infusion over a period of 60 minutes. Local reactions are more frequent if the infusion time is 30 minutes or less or if small veins of the hand are used. These local skin reactions may resolve upon completion of the infusion. Subsequent intravenous administration is not contraindicated unless the reactions recur or worsen.

Severe cutaneous adverse reactions
Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN: also known as Lyell's syndrome), Stevens Johnson syndrome (SJS), Acute Generalised Exanthematous Pustulosis (AGEP) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), which could be life-threatening or fatal, have been reported with CIPROBAY (see section 4.8). At the time of prescription, patients should be advised of the signs and symptoms of severe skin reactions and be closely monitored. If signs and symptoms suggestive of these reactions appear, CIPROBAY should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN, AGEP or DRESS with the use of CIPROBAY, treatment with CIPROBAY must not be restarted in this patient at any time.

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.

Influence on laboratory parameters/urinary sediment
CIPROBAY 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.

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

Sucrose load for suspension formulation
CIPROBAY oral suspension contains sucrose. It is thus unsuitable for patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency.

4.5. Interaction with other medicines and other forms of interactions

Medicines known to prolong QT interval

CIPROBAY 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 (oral) 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. Consequently, CIPROBAY should be administered either 1-2 hours before, or at least 4 hours after these preparations. The restriction does not apply to antacids belonging to the class of H_2 receptor blockers.

Food and Dairy Products
The concurrent administration of dairy products or mineral fortified drinks alone (e.g. milk, yoghurt, calcium fortified orange juice) and CIPROBAY should be avoided because the absorption of CIPROBAY is reduced. Dietary calcium as part of a meal, however, does not significantly affect absorption.

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

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

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 section 4.4). Tizanidine-containing medicines must not be administered together with CIPROBAY (see section 4.5).

Theophylline
Concurrent administration of CIPROBAY 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* in section 4.4).

Other xanthine derivatives
Concurrent administration of CIPROBAY 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 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 is discontinued in patients receiving both agents, monitoring of phenytoin therapy, including phenytoin serum-concentration measurements, is recommended during and shortly after co-administration of CIPROBAY with phenytoin.

Methotrexate

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

NSAID
Concomitant administration of the nonsteroidal anti-inflammatory medicines with quinolones such as CIPROBAY 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 with a vitamin K antagonist may augment its anticoagulant effects. The risk may vary with the underlying infection, age and general status of the patient, so that the contribution of ciprofloxacin to the increase in INR (international normalised ratio) is difficult to assess. The INR should be monitored frequently during and shortly after co-administration of CIPROBAY with a vitamin K antagonist (e.g. warfarin).

Duloxetine
An increase of duloxetine blood concentrations can be expected with concomitant administration with CIPROBAY (see *Cytochrome P450* in section 4.4).

Ropinirole
Concomitant use of ropinirole with ciprofloxacin as in CIPROBAY, 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 and/or dose adjustment as appropriate is recommended during and shortly after co-administration with CIPROBAY (see *Cytochrome P450* in section 4.4).

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

Clozapine
Following concomitant administration of 250 mg CIPROBAY with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased by 29 % and 31 %, respectively. Clinical surveillance and appropriate adjustment of clozapine dosage during and shortly after co-administration with CIPROBAY are advised (see *Cytochrome P450* in section 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 CIPROBAY. Caution is advised when prescribing CIPROBAY concomitantly with sildenafil.

ACE inhibitors and angiotensin-receptor blockers
Concomitant use of fluoroquinolones and ACE inhibitors/angiotensin-receptor blockers may precipitate acute kidney injury. The mechanism of the possible interaction between the different classes of medicines, over and above different mechanisms of kidney damage, is unknown (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 CIPROBAY may increase blood levels of zolpidem, concurrent use is not recommended.

4.6. Pregnancy and lactation

Safety during pregnancy and lactation has not been established (see section 4.3).

Pregnancy
The safety of CIPROBAY in pregnant women has not been established (see section 4.3). CIPROBAY must not be prescribed to pregnant women. Animal studies have demonstrated that CIPROBAY may damage the articular cartilage in the foetus.

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

4.7. Effects on ability to drive and use machines

Fluoroquinolones, including CIPROBAY 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

The frequencies of side effects reported with CIPROBAY in all clinical studies are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

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

System Organ Class	Common	Uncommon	Rare	Very Rare
Infections and Infestations		Candida and other fungal infections	Antibiotic associated 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

System Organ Class	Common	Uncommon	Rare	Very Rare
Immune System Disorders			Allergic reaction Allergic oedema / angioedema	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 ideation / thoughts and attempted or completed suicide) Hallucinations	Psychotic reactions (potentially culminating in self-injurious behaviour such as suicidal ideation / thoughts and attempted or completed suicide)
Nervous System Disorders		Headache Dizziness Sleep disorders Taste disorders	Paraesthesia Dysaesthesia Hypoaesthesia Tremor Seizures (including status epilepticus) Vertigo	Migraine Disturbed coordination Smell disorders Hyperaesthesia Intracranial hypertension Pseudotumour 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 Abdominal pain 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)

System Organ Class	Common	Uncommon	Rare	Very Rare
Skin and Subcutaneous Tissue Disorders		Rash Pruritus Urticaria	Photosensitivity reactions Blistering	Petechiae Erythema multiforme Erythema nodosum Stevens-Johnson syndrome (potentially life-threatening) Toxic epidermal necrolysis (potentially life-threatening)
Musculoskeletal, Connective Tissue and Bone Disorders		Arthralgia	Myalgia Arthritis Increased muscle tone and cramping	Muscular weakness Tendonitis 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	Injection site reaction	Unspecific pain Feeling unwell Fever	Oedema Sweating (hyperhidrosis)	Gait disturbance
Investigations		Increase in blood alkaline phosphatase	Abnormal Prothrombin level (increased INR) Increased amylase	

The side effects identified only during post-marketing surveillance, and for which a frequency could not be estimated.
Metabolism and nutrition disorders: Hyperglycaemia, hypoglycaemic coma
Nervous system disorders: Peripheral neuropathy and polyneuropathy, Guillain-Barre syndrome
Cardiac disorders: QT prolongation, ventricular dysrhythmia, Torsades de Pointes*, aortic aneurysm and dissection
Skin and subcutaneous tissue disorders: Acute generalized exanthematous pustulosis (AGEP), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), Fixed drug eruption (see section 4.4.)

Investigations: Increased International Normalised Ratio (INR) (in patients treated with Vitamin K antagonist)
*These events were reported during the post-marketing period and were observed predominantly among patients with further risk factors for QT prolongation (see section 4.4).

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 valve and/or aortic valve regurgitation was diagnosed.

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

There have been very rare cases of the following side effects reported following treatment with other fluoroquinolones, which might possibly also occur during treatment with CIPROBAY: increased intracranial pressure (including pseudotumor cerebri), hypernatraemia, hypercalcaemia, haemolytic anaemia.

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

Additional information on special populations

Paediatric population

The incidence of arthropathy (arthralgia, arthritis), mentioned above, is referring to data collected in studies with adults. In children, arthropathy is reported to occur commonly (see section 4.4).

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 Med Safety APP (Medsafety X SAHPRA) and platform (who-umc.org) found on SAHPRA website.

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, renal function, including urinary pH and acidity should be monitored to prevent crystalluria. Patients should be kept well hydrated. Calcium or magnesium containing antacids may reduce the absorption of CIPROBAY in overdose. Only a small quantity of CIPROBAY (< 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 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.
CIPROBAY is ineffective against *Treponema pallidum*.

5.2. Pharmacokinetic properties

The pharmacokinetics of ciprofloxacin suspension is very similar to that of ciprofloxacin film-coated tablets.
Ciprofloxacin plasma levels are dose-related and peak 0,5 - 2 hours after oral dosing. The absolute oral bioavailability is approximately 70 % with no substantial loss by first pass metabolism.

Distribution of ciprofloxacin is wide and the volume of distribution high, indicating extensive tissue penetration. Ciprofloxacin is present in lung, skin, fat, muscle, cartilage and bone. It is also present in active form in the saliva, nasal and bronchial secretions, sputum, skin blister fluid, lymph, peritoneal fluid, bile secretions, prostatic secretions, cerebrospinal fluid and the aqueous humor.
Protein binding is low. 40 % to 50 % is excreted in urine as unchanged substance. Approximately 15 % of a single dose of ciprofloxacin is eliminated as metabolites.
Elimination occurs primarily by the kidneys and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 mL /minute.
The elimination half-life of unchanged ciprofloxacin is 3 - 5 hours. The elimination kinetics are linear; after repeated dosing at 12 hourly intervals and once steady state has been reached no accumulation occurs.

5.3. Preclinical safety data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

CIPROBAY tablets
Cellulose microcrystalline
Crospovidone
Hypromellose

Maize starch
Magnesium stearate
Polyethylene glycol
Silica colloidal anhydrous
Titanium dioxide (E171)

CIPROBAY IV
Lactic acid solution 20 %
Sodium chloride
Hydrochloric acid, concentrated
Water for injection

CIPROBAY SUSPENSION 5 %
Microcapsules
Hypromellose
Magnesium stearate
Polyacrylate dispersion 30 %
Polysorbate 20
Povidone

Diluent
Medium chain triglycerides
Purified water
Soya lecithin
Strawberry flavour (contains benzyl benzoate)
Sucrose

6.2. Incompatibilities

CIPROBAY IV
The CIPROBAY IV infusion solution is compatible with 0,9 % sodium chloride, Ringer solution and Ringer lactate solution, 5 % and 10 % glucose solutions, 10 % fructose solution, and 5 % glucose solution with 0,225 % NaCl or 0,45 % NaCl. When CIPROBAY infusion solutions are mixed with compatible infusion solutions, for microbiological reasons and light sensitivity these solutions should be administered shortly after admixture.
This medicine must not be mixed with other medicines except those mentioned above.
Unless compatibility with other solutions for infusion /medicines has been confirmed, the solution for infusion must always be administered separately. The visual signs of incompatibility are e.g. precipitation, clouding and discolouration.
Incompatibility appears with all solutions for infusion / medicines that are physically or chemically unstable at the pH of the solution (e.g. penicillins, heparin solutions), especially on combination with solutions adjusted to an alkaline pH (pH of the CIPROBAY solutions for infusion: 3,9 - 4,5).

CIPROBAY SUSPENSION 5 %
No additions should be made to the mixed final suspension.

6.3. Shelf life

CIPROBAY tablets
5 years

CIPROBAY IV
4 years.

CIPROBAY SUSPENSION 5 %
Shelf life as packaged for sale
2 years

Shelf life of the reconstituted oral suspension
14 days

6.4. Special precautions for storage

CIPROBAY tablets
Store at or below 25 °C.

CIPROBAY IV
Store at or below 30 °C.
At cool storage temperatures, precipitation may occur, which will re-dissolve at room temperature. It is therefore recommended not to store the infusion in a refrigerator.

CIPROBAY SUSPENSION 5 %
The individual components viz. microcapsules and suspension diluent should not be used after the expiration dates have been reached.
Microcapsules: Store at or below 25 °C.
Diluent: Store at or below 25 °C. Protect from freezing. Store in upright position.
When reconstituted as directed utilizing the individual components, the final mixed ready-to-use suspension is stable at room temperature (up to 25 °C) for 14 days. After this time the final mixed suspension should not be taken.

6.5. Nature and contents of container

CIPROBAY tablets
One of the following primary packaging materials is used:
Transparent colourless or white opaque PP/Aluminium blister
Transparent colourless or white opaque PVC/PVDC/Aluminium blister
Transparent colourless PVC/Aluminium blister
Aluminium/Aluminium blister

Pack size of 10 tablets

CIPROBAY IV
One of the following primary packaging materials is used:
Colourless type 2 glass bottle inside siliconized with gray siliconized chlorobutyl (foil clad PTFE) or bromobutyl stopper

Pack sizes: 50 mL, 100 mL and 200 mL glass infusion bottles.
Not all pack sizes may be marketed

CIPROBAY SUSPENSION 5 %

Microcapsules: 30 mL brown type 3 glass bottle with white opaque PP/PE screw cap (child-proof).
Diluent: 150 mL white HDPE bottle with child-proof and tamper-proof PP screw cap.
1 blue graduated measuring spoon.

Pack size: Packs with one brown glass bottle containing 7,95 g of microcapsules and one white HDPE bottle containing 93 mL of diluent. The pack size is provided with a blue plastic graduated measuring spoon.

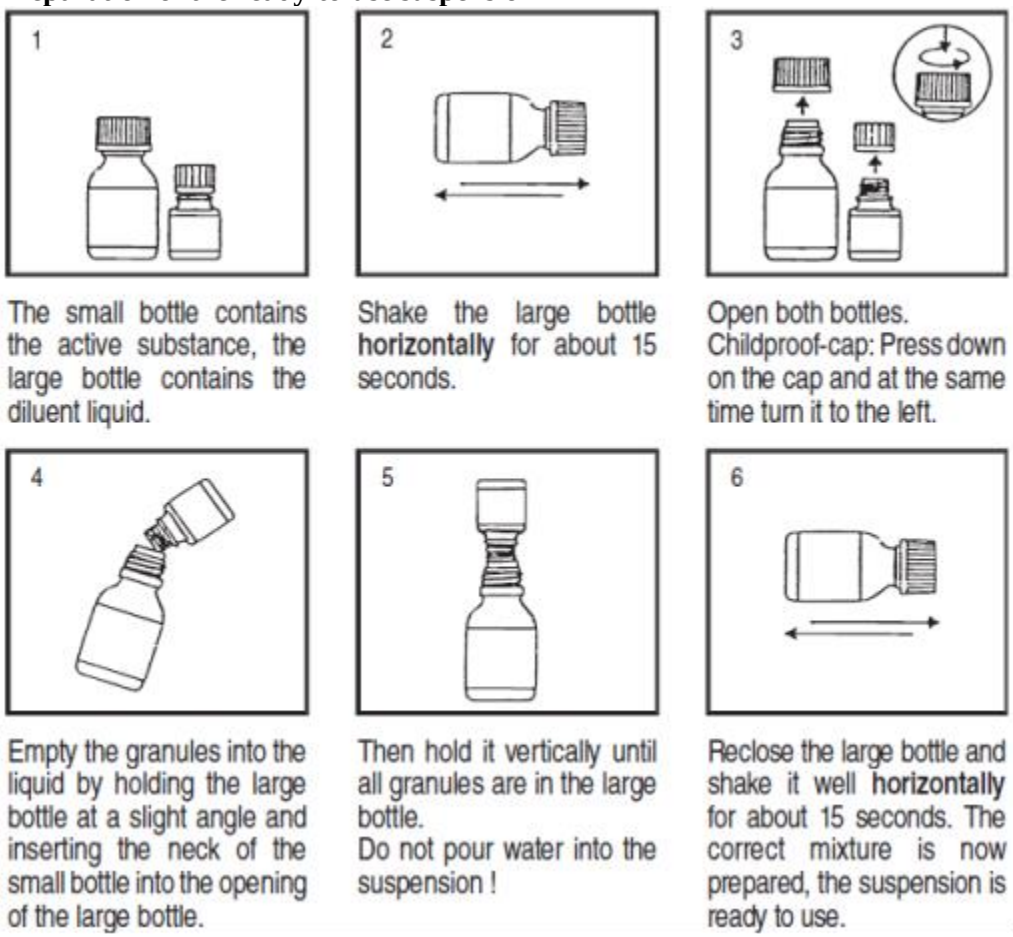
6.6. Special precautions for use and disposal

CIPROBAY IV
Any remaining solution should be discarded.

CIPROBAY IV is light-sensitive and should always be stored in the cardboard outer carton. No special precautions are, however, required during the 60 minute infusion period. In daylight conditions, efficacy is guaranteed for a period of 3 days.

At cool storage temperatures precipitation may occur, which will re-dissolve at room temperature (15 °C – 25 °C). It is therefore recommended not to store the infusion solution in a refrigerator.
The product should be inspected visually for particles prior to administration. Only clear solution free from particles should be used.

CIPROBAY SUSPENSION 5 %
Preparation of the ready-to-use suspension



Taking the ready-to-use suspension
Swallow the prescribed amount of suspension as quickly as possible. Do not chew the microcapsules present in the suspension, simply swallow them. A drink of water may be taken afterwards. Replace the cap on the bottle after use. It may be stored at room temperature up to 25 °C. Do not store in refrigerator. The ready-to-use suspension is stable for 14 days. After treatment has been completed, it should not be re-used.

Shake well each time before use for approx. 15 seconds.
The graduated measuring spoon with the markings 1/2 is equivalent to 2,6 mL and contains 2,5 mL of final mixed suspension and 1/1 is equivalent to 5,2 mL and contains 5,0 mL of final mixed suspension. The graduated measuring spoon must be used for measuring the required prescribed amount of CIPROBAY SUSPENSION.

After use the graduated measuring spoon should be cleaned under running water with dishwashing detergent, rinsed with water and dried thoroughly afterwards with a clean paper towel. The spoon should be stored with the CIPROBAY SUSPENSION 5 % bottle in the outer carton.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
Isando
1609
+27 (0)11 921 5911

8. REGISTRATION NUMBER

CIPROBAY 500:	U/20.1.1/127
CIPROBAY IV:	Y/20.1.1/311
CIPROBAY SUSPENSION 5 %:	31/20.1.1/0111
DILUENT FOR CIPROBAY SUSPENSION 5 % AND 10 %:	31/34/0113

9. DATE OF FIRST AUTHORISATION

CIPROBAY 500:	12 June 1990
CIPROBAY IV:	28 March 1991
CIPROBAY SUSPENSION 5 %:	28 March 1991
DILUENT FOR CIPROBAY SUSPENSION 5 % AND 10 %:	12 February 1997

10. DATE OF REVISION OF THE TEXT

14 January 2025

Botswana	
Ciprobay 500:	(S2) B9300975
Ciprobay IV:	(S2) B9300985
Namibia	
Ciprobay 500:	NS2 04/20.1.1/0351
Ciprobay Suspension 5%:	NS2 04/20.1.1/0355

Ciprobay IV:	NS2 04/20.1.1/0353
Zimbabwe	
Ciprobay 500:	(PP) 94/7.2.5/2874
Ciprobay Suspension 5%:	(PP) 2018/7.2.5/5544