Professional Information for CIPLOXX 250 / 500 / 750 (TABLETS)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CIPLOXX 250 (Tablets)

CIPLOXX 500 (Tablets)

CIPLOXX 750 (Tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CIPLOXX 250: Each tablet contains ciprofloxacin hydrochloride equivalent to 250 mg of ciprofloxacin.

CIPLOXX 500: Each tablet contains ciprofloxacin hydrochloride equivalent to 500 mg of ciprofloxacin.

CIPLOXX 750: Each tablet contains ciprofloxacin hydrochloride equivalent to 750 mg of ciprofloxacin.

For a full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM

CIPLOXX 250: White, film-coated, circular, biconvex tablet, plain on one face and with a deep score and ‘CP 250' debossed on the other face.

CIPLOXX 500: White, film-coated, capsule-shaped, biconvex tablet, plain on one side with a break line and ‘CP 500’ debossed on the face .

CIPLOXX 750: White, film-coated, capsule-shaped, biconvex tablet, plain on both sides. Coating intact.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CIPLOXX 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.

CIPLOXX 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.

CIPLOXX is indicated for the treatment of the following 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 influenzae*, *Haemophilus parainfluenzae*.

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*, *Streptococcus faecalis*.

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 aureus*, *Staphylococcus epidermidis*, *Streptococcus pyogenes*.

Severe and/or complicated gastrointestinal 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.

Gonorrhoea

CIPLOXX is ineffective against *Treponema pallidum* (see **section 5.1. "Inherently resistant organisms")**.

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 CIPLOXX. Therapy with CIPLOXX 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

The dosage range is 250 to 750 mg twice daily. The duration of treatment to contain and eradicate 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 the infection.

Infections of the lower respiratory tract

Severe and/or complicated:	750 mg twice daily.
In cystic fibrosis patients:	750 mg twice daily. The low body mass of these patients should, however, be taken into consideration when determining the dosage (7,5 to 15 mg/kg/day).

Infections of the urinary tract

Severe and/or complicated: 500 mg twice daily.

Infections of the skin

Severe and/or complicated: 750 mg twice daily.

Infectious diarrhoea 500 mg twice daily.

Bone infections

Severe and/or complicated: 750 mg twice daily. Treatment may be required for 4 to 6 weeks or longer.

Gonorrhoea: A single dose of 250 mg.

Special populations

Elderly

Elderly patients should be treated with the lowest possible dose; this will depend on the creatinine clearance and on the severity of the illness.

If the patient is unable to take oral ciprofloxacin, as in CIPLOXX, due to the severity of the illness or for other reasons (e.g. patients on enteral nutrition), it is recommended to start treatment with intravenous ciprofloxacin. Following intravenous administration, the treatment may be continued orally.

Impaired renal or liver function

In patients with reduced renal function, the half-life of CIPLOXX may be prolonged. The dosage needs to be adjusted as shown below.

For patients with changing renal function, or patients with renal impairment and hepatic insufficiency, monitoring of medicine serum levels provides the most reliable basis for dose

adjustment.

Dose adjustment of ciprofloxacin, as in CIPLOXX, for patients with renal and/or hepatic impairment:

1. **Renal insufficiency:**

	Creatinine clearance (CLcr) **(mL/min/1,73 m^2)**	**Dose**
1.1	31 ≤ CLcr ≤ 60	Maximum 1000 mg/day orally
1.2	CLcr ≤ 30	Maximum 500 mg/day orally
1.3	Impaired renal function and haemodialysis	As in 1.2 above; on dialysis days after dialysis.

2. **Renal impairment and CAPD (chronic ambulatory peritoneal dialysis):**
   2.1. Oral administration of CIPLOXX tablets as 1 x 500 mg tablet or 2 x 250 mg tablets are indicated.
   2.2. For CAPD patients with peritonitis, the recommended daily oral dose is 500 mg four times a day.
3. **Hepatic impairment:** No dose adjustment.
4. **Hepatic and renal impairment:** As in 1.1 and 1.2 above.

Method of administration

CIPLOXX tablets should be swallowed whole with plenty of liquid and may be taken with or without meals. If CIPLOXX is taken on an empty stomach, the active substance is absorbed more rapidly.

If taken with dairy products or with mineral fortified drinks, reduced absorption of CIPLOXX

may be expected. CIPLOXX should not be taken concurrently with dairy products or with mineral fortified drinks alone (e.g. yoghurt, milk, calcium fortified orange juice). Dietary calcium as part of a meal, however, does not significantly affect absorption.

4.3 Contraindications

CIPLOXX is contraindicated in children under the age of 18 years and in growing adolescents. Experimental evidence indicates that species variable reversible lesions of the cartilage of weight-bearing joints have occurred in immature members of certain animal species.

CIPLOXX is contraindicated in:

- Patients with a history of hypersensitivity to ciprofloxacin, any other quinolones, or any of the inactive ingredients of CIPLOXX.
- Pregnancy and lactation (see **section 4.6**).
- Patients receiving tizanidine concomitantly (see **section 4.5**).
- Concomitant use of fluoroquinolones with ACE inhibitors / angiotensin receptor blockers in patients with moderate to severe renal impairment and in the elderly.
- 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 be 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, nerve, 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.

- 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.

4.4 Special warnings and precautions for use

Streptococcal infections (including *Streptococcus pneumoniae*)

CIPLOXX is not recommended for the treatment of streptococcal infections due to inadequate efficacy.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) including toxic epidermal necrolysis (TEN) Stevens Johnson syndrome (SJS) and drug reaction with eosinophilia and systemic symptoms (DRESS), which could be life-threatening or fatal, have been reported with CIPLOXX (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, CIPLOXX should be discontinued immediately, and an alternative treatment should be considered. If the patient has developed a serious reaction such as SJS, TEN or DRESS with the use of CIPLOXX, treatment with CIPLOXX must not be restarted in this patient at any time.

Severe infections and/or infections due to Gram-positive or anaerobic bacteria

Monotherapy with CIPLOXX is not suited for treatment of severe infections and infections that may be due to Gram-positive or anaerobic pathogens. CIPLOXX must be co-administered with other appropriate antibacterial medicines in such infections. **CIPLOXX should not be used in staphylococcal infections and infections involving anaerobic bacteria.**

Genital tract infections

Gonococcal urethritis, epididymo-orchitis, cervicitis and pelvic inflammatory diseases may be caused by fluoroquinolone-resistant isolates of *Neisseria gonorrhoeae*. Therefore, CIPLOXX should only be used for the treatment of gonococcal urethritis or cervicitis if ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded.

For epididymo-orchitis and pelvic inflammatory diseases, empirical ciprofloxacin, as in CIPLOXX, should only be considered in combination with another suitable antibacterial medicine (such as a cephalosporin), unless ciprofloxacin-resistant *Neisseria gonorrhoeae* can be excluded. The treatment should be reconsidered if clinical improvement is not achieved after 3 days of treatment.

Urinary tract infections

Resistance of *Escherichia coli* (the most common pathogen involved in urinary tract infections) to fluoroquinolones, including CIPLOXX, varies. Prescribers are advised to take the local prevalence of resistance into consideration.

Intra-abdominal infections

There is limited data available on the efficacy of CIPLOXX in the treatment of post- surgical intra-abdominal infections.

Travellers' diarrhoea

The resistance of relevant pathogens to ciprofloxacin, as in CIPLOXX, in the countries visited should be taken into consideration.

Infections of the bones and joints

Depending on microbiological results, CIPLOXX should be used in combination with other antimicrobial medicines.

Complicated urinary tract infections and pyelonephritis

Treatment of urinary tract infections with CIPLOXX should be considered when other treatments cannot be used and should be based on microbiological results.

Other specific severe infections

CIPLOXX may be used in other severe infections, when other treatments cannot be used, or after failure of conventional therapy and when the microbiological results can justify the use of CIPLOXX, in accordance with official guidance, or after careful benefit-risk evaluation.

The use of CIPLOXX for specific severe infections other than those mentioned above has not been evaluated and clinical experience is limited.

Hypersensitivity

Anaphylactic / anaphylactoid reactions can occur (e.g. facial, vascular and laryngeal oedema, dyspnoea progressing to life-threatening shock), in some instances after the first administration. In these cases, CIPLOXX should be discontinued and appropriate medical treatment instituted (see **section 4.8**).

Children and adolescents

CIPLOXX is contraindicated in children less than 18 years. In children arthropathy is reported to occur commonly (see additional information on special populations).

Musculoskeletal system

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

CIPLOXX 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**). However, in very rare instances, after microbiological testing and evaluation of the risk / benefit balance, CIPLOXX may be used in these patients for the treatment of certain severe infections, particularly in the event of standard treatment failure or bacterial resistance.
Tendinitis and tendon rupture (especially of the Achilles tendon), sometimes bilateral, may occur with CIPLOXX, even within the first 48 hours of treatment. Tendon inflammation and ruptures may occur up to several months after CIPLOXX discontinuation. The risk of tendinopathy may be increased in elderly patients or in patients concomitantly treated with corticosteroids (see **section 4.5**)

CIPLOXX should be discontinued at any sign of tendinitis (e.g. painful swelling, inflammation). Care should be taken to keep the affected limb at rest. Physical exercise should be avoided, and a medical practitioner consulted.

Photosensitivity

CIPLOXX has been shown to cause photosensitivity reactions. Patients should be advised to avoid direct exposure to excessive sunlight or UV-light while taking CIPLOXX. If photosensitisation (i.e. sunburn-like skin reactions) occurs, treatment should be discontinued (see **section 4.8**).

Central nervous system

CIPLOXX should be used with caution in patients with a history of convulsive disorders.
CIPLOXX is known to trigger seizures or lower the seizure threshold. Cases of status epilepticus have been reported.

In epileptic patients and patients who have suffered from previous CNS disorders (e.g. previous history of convulsion, lowered convulsion threshold, reduced cerebral blood flow, stroke or altered brain structure), CIPLOXX 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 **section 4.3** and **section 4.8**). CIPLOXX should only be used where the benefits exceed the risks, as these patients have an increased risk of possible central nervous system side effects. If seizures occur, CIPLOXX should be discontinued (see **section 4.8**).

In some instances, CNS reactions occurred after the first administration of CIPLOXX. Depression or psychosis can rarely progress to suicidal ideation / thoughts culminating in attempted suicide or completed suicide. In these cases, CIPLOXX must be discontinued and the medical practitioner informed immediately.
In patients receiving CIPLOXX, cases of polyneuropathy (based on neurological symptoms including pain, burning, muscle weakness or sensory disturbances, alone or in combination) have been reported. In order to prevent the development of an irreversible condition,

CIPLOXX should be discontinued in patients experiencing symptoms of neuropathy, such as pain, tingling, burning, numbness, and/or weakness (see **section 4.8**).

Cardiac disorders

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 aneurysm disease, or in patients diagnosed with pre-existing aortic aneurysm and/or aortic dissection, or in presence of other risk factors or conditions predisposing for aortic aneurysm and dissection (e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension, known atherosclerosis).

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

CIPLOXX has been associated with QT prolongation (see **sections 4.2** and **4.8**).

Concomitant use of CIPLOXX 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/or dissection after intake of fluoroquinolones, particularly in the elderly population. Fluoroquinolones, such as

CIPLOXX, should only be used in patients at risk if no other treatment options are available (see **section 4.3**).

Patients at risk are patients with a positive family history of aneurysmal disease, pre- existing aortic disease and/or dissection or other risk factors or conditions predisposing to aortic aneurysm and dissection e.g. Marfan syndrome, vascular Ehlers-Danlos syndrome, Takayasu arteritis, giant cell arteritis, Behcet's disease, hypertension and known atherosclerosis.

In case of sudden abdominal, chest or back pain, patients should be advised to immediately go to their medical practitioner or a hospital emergency department.

There is some evidence, although inconclusive, of a possible association between oral fluoroquinolone use, such as CIPLOXX, and mitral valve and/or aortic valve regurgitation. A thorough cardiovascular examination including an echocardiogram, should be performed before oral fluoroquinolones are prescribed. Fluoroquinolones, including CIPLOXX, should not be prescribed to patients with mitral valve and/or aortic valve regurgitation (see **section 4.3**).

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 initiation of treatment and monitored during treatment with fluoroquinolones and ACE inhibitors / angiotensin receptor blockers.

Women and the elderly may be more sensitive to QTc-prolonging medicines. Therefore, caution should be taken when fluoroquinolones, including CIPLOXX, are administered in these populations (see **section 4.2** and **section 4.8**)

Disturbances in blood glucose

Disturbances in blood glucose, including both hyperglycaemia and hypoglycaemia have

been reported, usually in diabetic patients receiving concomitant treatment with an oral hypoglycaemic medicine or with insulin, and in the elderly. Cases of hypoglycaemic coma have been reported. In diabetic patients, careful monitoring of blood glucose is recommended (see **section 4.5**. and **section 4.8**).

Gastrointestinal system

The development of severe and persistent diarrhoea during or after treatment (including several weeks after treatment), may indicate pseudomembranous colitis, which may be life-threatening with possible fatal outcome, and requires immediate treatment (see **section 4.8**). In such cases, CIPLOXX must be discontinued immediately and appropriate therapy initiated (e.g. vancomycin, orally 4 x 250 mg/day). In this situation, anti-peristaltic medicines are contraindicated.

Renal and urinary system

Crystalluria has occurred with the use of CIPLOXX. Patients receiving CIPLOXX should be well hydrated and excessive alkalinity of the urine should be avoided.

Impaired renal function

In patients with impaired renal function, dosage adjustment is needed to avoid an increase in adverse reactions due to accumulation of CIPLOXX, since ciprofloxacin is largely excreted unchanged via renal pathway (see **section 4.2**).

Concomitant use of fluoroquinolones, such as CIPLOXX, 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 CIPLOXX and ACE inhibitors / angiotensin receptor blockers.

Hepatobiliary system

Hepatic necrosis and life-threatening hepatic failure have been reported with CIPLOXX (see **section 4.8**). Treatment should be discontinued if any signs or symptoms of hepatic disease develop, such as jaundice, anorexia, dark urine, tender abdomen or pruritus. There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage.

Glucose-6-phosphate dehydrogenase deficiency

In patients with glucose-6-phosphate dehydrogenase deficiency, haemolytic reactions have been reported with CIPLOXX. Unless the benefit is considered to outweigh the risk, CIPLOXX should be avoided in these patients. The potential occurrence of haemolysis should be monitored.

Resistance

Long-term or repeated administration of CIPLOXX can lead to superinfections with resistant bacteria or fungi.

During or following a course of treatment with CIPLOXX, bacteria that demonstrate resistance to ciprofloxacin may be isolated, with or without a clinically apparent superinfection. There may be a particular risk of selecting for ciprofloxacin-resistant bacteria during extended durations of treatment and when treating nosocomial infections and/or infections caused by Staphylococcus and Pseudomonas species.

Cytochrome P450

CIPLOXX inhibits CYP1A2 and may therefore cause increased serum concentrations of concomitantly administered medicines metabolised by this enzyme (e.g. tizanidine, theophylline, olanzapine, clozapine, ropinirole, duloxetine, agomelatine). Co-administration of CIPLOXX and tizanidine is contraindicated (see **section 4.3**). Therefore, patients taking these medicines concurrently with CIPLOXX should be monitored closely for signs of overdose, and determination of serum concentrations (e.g. of theophylline) may be required (see **section 4.5**).

Methotrexate

Concurrent administration with methotrexate may increase methotrexate concentrations to toxic levels and is not recommended.

Interaction with tests

In specimens from patients currently taking CIPLOXX, the *in vitro* activity of CIPLOXX against *Mycobacterium tuberculosis* may give false negative bacteriological test results.

Influence on laboratory parameters / urinary sediment

There can be a temporary increase in transaminases, alkaline phosphatase or cholestatic jaundice, especially in patients with previous liver damage, temporary increase in urea, creatinine or bilirubin in the serum; in individual cases hypoglycaemia, hyperglycaemia, crystalluria or haematuria may occur.

Pancytopenia and marrow depression are side effects that may be potentially life-threatening (see **section 4.8**).

Vision disorders

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

4.5 Interactions with other medicines and other forms of interaction

Effects of other medicines on CIPLOXX

Medicines known to prolong QT interval

CIPLOXX should be used with care in patients receiving medicines known to prolong QT interval (e.g. Class IA and III antidysrhythmics, macrolides, tricyclic antidepressants, antipsychotics) (see **section 4.3**).

Chelation complex formation

CIPLOXX tablets should be administered 1 to 2 hours before, or at least 4 hours after taking multivalent cation-containing medicines and mineral supplements, (e.g. magnesium, calcium, aluminium or iron preparations), antacids or sucralfate, polymeric phosphate binders (e.g. sevelamer or lanthanum carbonate), and highly buffered medicines (e.g. didanosine or other antiretrovirals) containing aluminium, magnesium or calcium, as interference with absorption may occur. This restriction does not apply to antacids belonging to the class of H2-receptor blockers.

Food and dairy products

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

Non-steroidal anti-inflammatory medicines (NSAIDs)

Concomitant administration of the non-steroidal anti-inflammatory medicine fenbufen with quinolones may increase the risk of central nervous system stimulation and seizures.

Probenecid

Probenecid interferes with renal secretion of CIPLOXX. Co-administration of probenecid and CIPLOXX increases the CIPLOXX serum concentrations.

Metoclopramide

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

Omeprazole

Co-administration of CIPLOXX and omeprazole results in a 20 % reduction of the Cmax and AUC of CIPLOXX.

Effects of CIPLOXX on other medicines

Tizanidine

Tizanidine must not be co-administered with CIPLOXX (see **section 4.3**), as it increases serum tizanidine concentrations (7-fold increase in Cmax, 10-fold increase in AUC, on average). Increased serum tizanidine concentrations are associated with potentiation of hypotensive and sedative effects.

Agomelatine

Fluvoxamine, a strong inhibitor of CYP450 1A2, markedly inhibits the metabolism of agomelatine resulting in a 60-fold increase of agomelatine exposure. Although no data are available for CIPLOXX, a moderate inhibitor of CYP450 1A2, similar effects may be expected (see **section 4.4**).

Zolpidem

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

Methotrexate

Renal tubular transport of methotrexate may be inhibited by co-administration of CIPLOXX, potentially resulting in increased methotrexate plasma levels and an increased risk of methotrexate associated toxic reactions. Therefore, patients receiving treatment with methotrexate should be carefully monitored when concomitant treatment with CIPLOXX is indicated. Concomitant use is, however, not recommended (see **section 4.4**).

Theophylline

Concurrent administration of CIPLOXX with theophylline may lead to elevated plasma concentrations of theophylline and prolongation of its elimination half-life. This may result in increased risk of theophylline-related toxicity and may rarely be life-threatening or fatal. If concomitant use cannot be avoided, plasma levels of theophylline should be monitored, and dosage adjustments made as appropriate (see **section 4.4**).

Other xanthine derivatives

Co-administration of CIPLOXX and caffeine or pentoxifylline (oxpentifylline), caused raised serum concentrations of these xanthine derivatives.

Phenytoin

Simultaneous administration of phenytoin and CIPLOXX may cause increased or reduced phenytoin serum levels, to such an extent that monitoring of medicine levels is recommended.

Ciclosporin

Frequent monitoring of serum creatinine concentrations (twice a week) is advised in patients on concomitant ciclosporin therapy, as transient increases in serum creatinine concentrations have been observed.

Vitamin K antagonists

The simultaneous administration of CIPLOXX and warfarin (a vitamin K antagonist) may augment its anticoagulant effects. The risk may vary with the underlying infection, general status and age of the patient so that it is difficult to assess the contribution of CIPLOXX to the increase in INR (international normalised ratio). Therefore, the INR should be closely monitored during and shortly after co- administration.

Glibenclamide

Concurrent administration of CIPLOXX and glibenclamide can potentiate the action of glibenclamide, leading to hypoglycaemia (see **section 4.4**)

Duloxetine

Concurrent use of duloxetine with strong inhibitors of the CYP450 1A2 isozyme, such as fluvoxamine, may result in an increase of AUC and Cmax of duloxetine. Although no data are available on a possible interaction with CIPLOXX, similar effects may be expected with co-administration (see **section 4.4**)

Ropinirole

Concurrent use of ropinirole with CIPLOXX, a moderate inhibitor of the CYP450 1A2 isozyme, results in an increase in ropinirole Cmax of 60 % and AUC of 84 %. During and shortly after co-administration with CIPLOXX, monitoring of ropinirole-related side effects and dose adjustment, if required, are recommended (see **section 4.4**).

Lidocaine (lignocaine)

Concurrent use of lidocaine (lignocaine) containing medicines with CIPLOXX, a moderate inhibitor of CYP450 1A2 isozyme, reduces clearance of intravenous lidocaine by 22 %. Although lidocaine treatment was well tolerated, a possible interaction with CIPLOXX, associated with side effects may occur upon co- administration.

Clozapine

After co-administration of 250 mg ciprofloxacin, as in CIPLOXX, with clozapine for 7 days, serum concentrations of clozapine and N-desmethylclozapine were increased

by 29 % and 31 %, respectively. During and shortly after co-administration with CIPLOXX, clinical surveillance and appropriate adjustment of clozapine dosage are advised (see **section 4.4**).

Sildenafil:

Following an oral dose of 50 mg sildenafil given concurrently with 500 mg ciprofloxacin, as in CIPLOXX, in healthy subjects, sildenafil C_{max} and AUC were increased about two-fold. Therefore, care should be taken when prescribing CIPLOXX with sildenafil, taking into consideration the risks and the benefits.

ACE inhibitors / renin-angiotensin receptor blockers:

Concomitant use of fluoroquinolones, such as CIPLOXX, and ACE inhibitors / angiotensin receptor blockers may precipitate acute kidney injury (see **section 4.3**). Careful consideration should be given to age, renal function, hydration status and concomitant prescribing of diuretics or NSAIDs, and to monitoring of changes in renal function throughout treatment.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety in pregnancy has not been established (see **section 4.3**).

Breastfeeding

CIPLOXX is excreted in breast milk. Due to the potential risk of articular damage, CIPLOXX should not be used during lactation.

4.7 Effects on ability to drive and use machines

Due to its neurological effects, CIPLOXX may affect reaction time. The ability to drive a motor vehicle or operate machinery may be impaired by CIPLOXX, even when taken as prescribed. This applies particularly in combination with alcohol.

4.8 Undesirable effects

Infections and infestations

Frequent	Moniliasis.
Less frequent:	Mycotic superinfections, pseudomembranous colitis.

Blood and lymphatic system disorders

Frequent:	Eosinophilia, leukopenia.
Less frequent	Granulocytopenia, anaemia, thrombocytopenia, leucocytosis, thrombocytemia (thrombocytosis) haemolytic anaemia, altered prothrombin values, pancytopenia (life-threatening), bone marrow suppression (life-threatening), neutropenia, agranulocytosis.

Immune system disorders

Less frequent:	Allergic reaction, medicine fever, anaphylactoid (anaphylactic) reaction, anaphylactic shock (life- threatening), pruritic rash, allergic oedema / angioedema, serum sickness-like reaction.

Metabolism and nutrition disorders

Less frequent:	Hyperglycaemia, hypoglycaemia, particularly in diabetic patients (see **section 4.4** and **section 4.5**).

Psychiatric disorders

Frequent: Insomnia, agitation, confusion.

Less frequent: Anxiety reaction, abnormal dreams (nightmares), hallucinations, psychotic reactions (potentially culminating in suicidal ideation or suicide attempts and completed suicide) depression (potentially culminating in suicidal ideation or suicide attempts and completed suicide) psychomotor hyperactivity, disorientation, sleep disorders.

Nervous system disorders

Frequent: Dizziness, headache, taste perversion.

Less frequent: Paraesthesias (peripheral paralgesia), unsteady gait, convulsions, grand mal convulsion, including status epilepticus, intracranial hypertension and pseudotumour cerebri tremor (trembling), hypaesthesia, taste loss (impaired taste) dysaesthesia, migraine, disturbed coordination, olfactory nerve disorders.

Frequency unknown: Peripheral neuropathy, polyneuropathy.

Eye disorders

Less frequent Abnormal vision (visual disturbances), e.g. diplopia, chromatopsia.

Ear and labyrinth disorders

Less frequent: Tinnitus, transient deafness / impairment of hearing (especially at high frequencies), hearing loss, vertigo.

Cardiac disorders

Less frequent: Tachycardia.

Frequency unknown: Ventricular dysrhythmia, torsades de pointes (reported

predominantly in patients with risk factors for QT prolongation), prolonged ECG QT.

Vascular disorders

Frequent: Thrombo-phlebitis.

Less frequent: Vasodilation (flushing) syncope, hypotension, oedema peripheral, vascular, face, vasculitis.

Respiratory, thoracic and mediastinal disorders

Less frequent: Dyspnoea (including asthmatic condition), larynx oedema.

Gastrointestinal disorders

Frequent: Nausea, diarrhoea, vomiting, dyspepsia, abdominal pain, anorexia, flatulence.

Less frequent: Moniliasis (oral and gastrointestinal), gastrointestinal pains, pancreatitis, decreased appetite.

Hepatobiliary disorders

Frequent: Increased alkaline phosphatase, abnormal liver function tests, bilirubinemia.

Less frequent: Cholestatic jaundice, jaundice, hepatitis, increased transaminases, hepatic impairment, cholestatic icterus, hepatic necrosis (very seldom progressing to life- threatening hepatic failure).

Skin and subcutaneous tissue disorders

Frequent: Rashes, urticaria, pruritus, maculopapular rash.

Less frequent: Photosensitivity reaction, erythema nodosum, erythema

multiforme (minor), Stevens-Johnson syndrome (potentially life-threatening), petechiae, haemorrhagic bullae, papules, crust formation with signs of vasculitis, toxic epidermal necrolysis (potentially life-threatening).

Frequency unknown: Acute generalised exanthematous pustulosis (AGEP), DRESS (medicine reaction with eosinophilia and systemic symptoms syndrome).

Musculoskeletal, connective tissue and bone disorders

Frequent: Joint pain (arthralgia).

Less frequent: Joint disorder (joint swelling), muscular weakness, myalgia / muscular pain, tendinitis, tendon rupture (predominantly Achilles tendon), musculoskeletal pain (e.g. extremity pain, back pain, chest pain), arthritis, increased muscle tone and cramping, exacerbation of symptoms of myasthenia gravis.

Renal and urinary disorders

Less frequent: Crystalluria, interstitial nephritis, tubulointerstitial nephritis, renal impairment, renal failure, haematuria, abnormal kidney function.

Reproductive system and breast disorders

Less frequent: Vaginal moniliasis.

General disorders and administrative site conditions

Frequent: Asthenia (general feeling of weakness, tiredness).

Less frequent: Pain, fever, sweating (hyperhidrosis).

Investigations

Frequent: Increased SGOT / AST, increased SGPT / ALT, increased creatinine, increased urea (BUN).

Less frequent: Increased amylase, increased lipase.

Frequency unknown: Increased INR (in patients treated with vitamin K antagonists).

Post-marketing

Infections and infestations

Less frequent: Life-threatening pseudomembranous colitis with possible fatal outcomes.

Blood and lymphatic system disorders

Less frequent: Petechia (punctate skin haemorrhages), pancytopenia, agranulocytosis, marrow depression.

Immune system disorders

Less frequent Serum sickness like reaction.

Metabolism and nutrition disorders

Frequency unknown: Hyperglycaemia, hypoglycaemic coma (see **section 4.4** and **section 4.5**).

Psychiatric disorders

Less frequent: Psychosis.

Nervous system disorders

Less frequent: Intracranial hypertension, ataxia, hyperesthesia, hypertonia, twitching, parosmia (impaired smell), anosmia

(usually reversible on discontinuation).

Cardiac disorders

Frequency unknown: Cases of mitral valve and/or aortic valve regurgitation were reported in patients treated with oral fluoroquinolones, such as CIPLOXX. 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 regurgitation cases was diagnosed.

Gastrointestinal disorders

Less frequent: Pancreatitis.

Hepatobiliary disorders

Less frequent: Liver necrosis (very seldom progressing to life-threatening hepatic failure).

Skin and subcutaneous tissue disorders

Less frequent: Stevens-Johnson syndrome, epidermal necrolysis (Lyell's syndrome), fixed eruption.

Musculoskeletal, connective tissue and bone disorders

Less frequent Tendinitis (predominantly achillotendinitis), partial or complete tendon rupture (predominantly Achilles tendon), myasthenia, exacerbation of symptoms of myasthenia gravis.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8 or to Cipla Medpro (Pty) Ltd by e-mail at drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Mild symptoms of toxicity have been reported with an overdose of 12 g. Acute renal failure has been reported with an acute overdose of 16 g. Symptoms of overdose are dizziness, headache, tremor, tiredness, hallucinations, seizures, confusion, renal and hepatic impairment, abdominal discomfort as well as crystalluria and haematuria. In the event of acute, excessive oral overdosage, reversible renal toxicity has been reported.

Apart from routine emergency measures, e.g. ventricular emptying followed by medical carbon, it is recommended to monitor renal function (including urinary pH, and to acidify to prevent crystalluria, if required). Patients should be kept well hydrated. Calcium or magnesium containing antacids may theoretically reduce the absorption of CIPLOXX in overdoses.

Only a small amount of ciprofloxacin, as in CIPLOXX, (< 10 %) is removed from the body after haemodialysis or peritoneal dialysis.

Treatment is symptomatic and supportive. Due to the possibility of QT interval prolongation, ECG monitoring should be undertaken.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1. Broad and medium spectrum antibiotics.

Mechanism of action

Ciprofloxacin is a synthetic, fluoroquinolone antibiotic. It is bactericidal and acts by inhibiting both type II topoisomerase (DNA-gyrase) and topoisomerase IV, which are essential in the reproduction of bacterial DNA (replication, transcription, repair and recombination).

It has *in vitro* bactericidal activity against gram-negative and gram-positive organisms (*in vitro* sensitivity does not necessarily imply *in vivo* efficacy).

Mechanism of resistance

Resistance to ciprofloxacin, *in vitro*, can be acquired in a stepwise process through mutation of target sites in both DNA gyrase and topoisomerase IV. A variable degree of cross-resistance between ciprofloxacin and other fluoroquinolones results. Single mutations may not result in clinical resistance, however multiple mutations usually result in clinical resistance to many or all medicines within the class.

Mechanisms of resistance, including impermeability and/or active substance efflux pump mechanisms, may have a variable effect on susceptibility to fluoroquinolones, which depends on the physiochemical properties of the various active substances within the class and the affinity of transport systems for each active substance. In clinical isolates, all *in vitro* mechanisms of resistance are frequently observed. Resistance mechanisms that inactivate other antibiotics, such as permeation barriers (common in *Pseudomonas aeruginosa)* and efflux mechanisms, may affect susceptibility to ciprofloxacin.

Plasmid-mediated resistance encoded by qnr-genes has been reported.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

Staphylococcus spp.

Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications. Methicillin-resistant *S. aureus* very commonly express co-resistance to fluoroquinolones. The rate of resistance to methicillin is around 20 to 50 % among all staphylococcal species and is usually higher in nosocomial isolates.

Aerobic Gram-negative micro-organisms

Acinetobacter baumannii

Enterobacter aerogenes Klebsiella oxytoca Providencia spp.

Pseudomonas fluorescens

Clinical efficacy has been demonstrated for susceptible isolates of the following organisms in approved clinical indications:

Burkholderia cepacia

Campylobacter spp.

Citrobacter freundii

Enterobacter cloacae

Escherichia coli Klebsiella

pneumonia Morganella

morganii Neisseria

gonorrhoeae Proteus

mirabilis Proteus vulgaris

Pseudomonas aeruginosa Serratia

marcescens

Anaerobic micro-organisms

Peptostreptococcus spp.

Propionibacterium acnes

Peptococcus spp.

Inherently resistant organisms

Aerobic Gram-positive micro-organisms

Actinomyces

Enterococcus faecium

Listeria monocytogenes

Nocardia asteroides

Aerobic Gram-negative micro-organisms

Stenotrophomonas maltophilia

Anaerobic micro-organisms

Excepted as listed above.

Bacteroides Treponema

pallidum

Other micro-organisms

Mycoplasma genitalium Ureaplasma

urealitycum

5.2 Pharmacokinetic properties

Absorption

After oral administration, ciprofloxacin is absorbed rapidly and extensively, primarily from the small intestine. Ciprofloxacin plasma levels are dose-related and peak at 0,5 to 2 hours.

Single doses of 100 to 750 mg produced dose-dependent maximum serum concentrations (Cmax) between 0,56 and 3,7 mg/L. Serum concentrations increase proportionately with

doses up to 1000 mg.

The absolute oral bioavailability is about 70 %, with first pass metabolism not causing a substantial loss.

A 500 mg oral dose, given every 12 hours, has been shown to produce an area under the serum concentration-time curve (AUC) equivalent to the AUC produced by an intravenous infusion of 400 mg ciprofloxacin, given over 60 minutes, every 12 hours.

Distribution

Protein binding is low. Ciprofloxacin is present in plasma mainly in a non-ionised form and has a large steady state volume of distribution of 2 to 3 L/kg body weight, indicating extensive tissue penetration.

Ciprofloxacin reaches high concentrations in tissues, such as lung (alveolar macrophages, epithelial fluid, biopsy tissue), sinuses, inflamed lesions (cantharides blister fluid) and the urogenital tract (prostate, urine, endometrium), where total concentrations exceeding those of plasma concentrations are attained.

Ciprofloxacin is present in fat, muscle, cartilage and bone. It is also present in active form in the saliva, lymph, peritoneal fluid, bile secretions, cerebrospinal fluid and the aqueous humor.

Biotransformation

Four metabolites have been reported in low concentrations, and were identified as: desethyleneciprofloxacin (M1), sulphociprofloxacin (M2), oxociprofloxacin (M3) and formylciprofloxacin (M4). *In vitro*, the metabolites display antimicrobial activity, but to a lower degree than the parent compound.

Ciprofloxacin is known to be a moderate inhibitor of the CYP450 1A2 isoenzymes.

Elimination

Forty to fifty percent is excreted in urine as unchanged ciprofloxacin. About 15 % of a single dose is eliminated as metabolites. Elimination is primarily renal and mainly during the first 12 hours after dosing. Renal clearance is approximately 300 mL/minute. Total body clearance is between 480 to 600 mL/kg/h.

The elimination half-life of unchanged ciprofloxacin is 3 to 5 hours. The elimination kinetics are linear. No accumulation occurs following repeated 12 hourly dosing and once steady state has been reached.

Ciprofloxacin undergoes both glomerular filtration and tubular secretion. Severely impaired renal function results in increased ciprofloxacin half-lives of up to 12 hours.

Non-renal clearance of ciprofloxacin is largely due to active trans-intestinal secretion and metabolism. One percent of the dose is excreted via the biliary route. Ciprofloxacin is present in the bile in high concentrations.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

colloidal silica

croscarmellose sodium

hypromellose

magnesium stearate

microcrystalline

cellulose polyethylene

glycol povidone

propylene

glycol purified talc

titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C. Keep blister strips in outer carton until required for use.

6.5 Nature and contents of container

CIPLOXX 250: Colourless, transparent PVC, aluminium blister packs of 6 and 10 tablets packed in a carton.

CIPLOXX 500: Colourless transparent PVC, aluminium blister packs of 10 tablets packed in a carton.

CIPLOXX 750: Colourless, transparent PVC, aluminium blister packs of 10 tablets packed in a carton.

6.6 Special precautions for disposal and other handling

No special instructions for use / handling.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD

Building 9

Parc du Cap

Mispel Street

Bellville 7530

8. REGISTRATION NUMBER(S)

CIPLOXX 250: 36/20.1.1/0376

CIPLOXX 500: 36/20.1.1/0377

CIPLOXX 750: 36/20.1.1/0378

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

24 January 2003

10. DATE OF REVISION OF THE TEXT

20 June 2023